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Abstract

Simvastatin to reduce pulmonary dysfunction in patients with acute respiratory distress syndrome: the HARP-2 RCT

Daniel F McAuley,[1,2,3]* John G Laffey,[4] Cecilia M O'Kane,[1] Gavin D Perkins,[5,6] Brian Mullan,[2] Thomas J Trinder,[7] Paul Johnston,[8] Phillip A Hopkins,[9] Andrew J Johnston,[10] Lynn Murphy,[3] Christine McNally,[3] Ashley M Agus,[3] Clíona McDowell,[3] Colette Jackson[3] and the HARP-2 investigators on behalf of the Irish Critical Care Trials

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Background: Acute lung injury is a common devastating clinical syndrome characterised by life-threatening respiratory failure requiring mechanical ventilation and multiple organ failure, and is a major cause of morbidity and mortality.

Objective: This study tested the hypothesis that treatment with simvastatin would improve clinical outcomes in patients with acute respiratory distress syndrome (ARDS).

Design: This was a multicentre, allocation-concealed, randomised, double-blind, parallel-group trial.

Setting/participants: Patients in intensive care units were eligible if they were intubated and mechanically ventilated and had ARDS as defined by a partial pressure of arterial oxygen to fraction of inspired oxygen concentration ($PaO_2 : FiO_2$) ratio of ≤ 300 mmHg, bilateral pulmonary infiltrates consistent with pulmonary oedema and no evidence of left atrial hypertension.

Intervention: Patients were randomised in a 1 : 1 ratio to receive enteral simvastatin 80 mg or identical placebo tablets once daily for up to 28 days.

Main outcome measures: The primary outcome was the number of ventilator-free days (VFDs) to day 28. Secondary outcomes included the number of non-pulmonary organ failure-free days to day 28, mortality and safety. The biological effect by which simvastatin may modify mechanisms implicated in the development of ARDS was also investigated. A cost-effectiveness analysis was also planned.

Results: The study was completed when 540 patients were recruited with 259 patients allocated to simvastatin and 281 patients to placebo, with 258 patients in the simvastatin group and 279 patients in the placebo group included in the analysis of the primary outcome. There was no significant difference between study groups in mean [standard deviation (SD)] VFDs [12.6 days (SD 9.9 days) with simvastatin and 11.5 days (SD 10.4 days) with placebo; mean difference 1.1, 95% confidence interval –0.6 to 2.8; $p = 0.21$], non-pulmonary organ failure-free days [19.4 days (SD 11.1 days) with simvastatin and 17.8 days (SD 11.7 days) with placebo; $p = 0.11$] or in 28-day mortality (22.0% with simvastatin and 26.8% with placebo; $p = 0.23$). There was no difference in the incidence of severe adverse events between the groups. Simvastatin did not significantly modulate any of the biological mechanisms investigated. Simvastatin was cost-effective at 1 year compared with placebo for the treatment of ARDS, being associated with both a small quality-adjusted life-year (QALY) gain and cost saving.

Limitations: One possibility for the lack of efficacy relates to the statin and dosage used. It is possible that adverse effects at the simvastatin dosage used outweighed a beneficial effect, although our data suggest that this is unlikely. The heterogenous cohort of patients with ARDS was an attempt to ensure that our findings would be generalisable; however, it may be more appropriate to target potential therapies based on their proposed biological mechanism for a specific population of patients. The assumptions underpinning the economic benefit are based on the analysis of a subgroup of responders.

Conclusions: High-dose enteral simvastatin, while safe and with minimal adverse effects, is not effective at improving clinical outcomes in patients with ARDS. There was a small gain in QALYs and a cost saving associated with simvastatin.

Future work: There is a need to confirm if ARDS endotypes that are more likely to benefit from targeted treatment with simvastatin exist. The potential role of simvastatin in the prevention of ARDS in patients at a high risk of developing ARDS has not yet been evaluated.

Trial registration: Current Controlled Trials ISRCTN88244364.

Funding: This project was funded by the Efficacy and Mechanism Evaluation programme, a Medical Research Council and National Institute for Health Research (NIHR) partnership. This study was also funded in the Republic of Ireland by the Health Research Board (HRA_POR-2010-131). In addition, the Health and Social Care Research and Development division of the Public Health Agency in Northern Ireland, the Intensive Care Society of Ireland and Randomized Exploratory Clinical Trial to Evaluate the Safety and Effectiveness of Stem Cell Product in Alcoholic Liver Cirrhosis Patient (REVIVE) provided additional funding.

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List of abbreviations

AE	adverse event
ALI	acute lung injury
ALT	alanine transaminase
Ang2	angiopoietin 2
APACHE II	Acute Physiology And Chronic Health Evaluation
AR	adverse reaction
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CK	creatine kinase
CMP	Case Mix Programme
CONSORT	Consolidated Standards of Reporting Trials
CREC	Clinical Research Ethics Committee
CRF	case report form
CRP	C-reactive protein
CTCAE	common terminology criteria for adverse events
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
EME	Efficacy and Mechanism Evaluation
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
GP	general practitioner
HARP-2	Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in Acute lung injury to Reduce Pulmonary dysfunction
HDU	high-dependency unit
HR	hazard ratio
HRB	health research board
HRQoL	health-related quality of life
ICCTG	Irish Critical Care Trials Group
ICER	incremental cost-effectiveness ratio
ICNARC	Intensive Care National Audit and Research Centre
ICU	intensive care unit
IL	interleukin
IMB	Irish Medicines Board
ISF	investigator site file
LPS	lipopolysaccharide
mCTA	model Clinical Trial Agreement
MHRA	Medicines and Healthcare Products Regulatory Agency
MMP	matrix metalloproteinase
MRC	Medical Research Council
NICE	National Institute for Health and Care Excellence
NICTU	Northern Ireland Clinical Trials Unit
NIHR	National Institute for Health Research
OFFD	oscillator frequency-free day
OI	oxygenation index
ORECNI	Office for Research Ethics Committees Northern Ireland
PAOP	pulmonary arterial occlusion pressure
PerLR	personal legal representative
PI	principal investigator
PIS	patient information sheet
ProfLR	professional legal representative
QALY	quality-adjusted life-year
R&D	research and development
RAGE	receptor for advanced glycation end-products
RCT	randomised controlled trial
REC	Research Ethics Committee

REVIVE	Randomized Exploratory Clinical Trial to Evaluate the Safety and Effectiveness of Stem Cell Product in Alcoholic Liver Cirrhosis Patient
SAE	serious adverse event
SAR	serious adverse reaction
SD	standard deviation
SOFA	sequential organ failure assessment
SPC	summary of product characteristics
SUSAR	suspected unexpected serious adverse reaction
TNF-α	tumour necrosis factor alpha
UAR	unexpected adverse reaction
VAS	visual analogue scale
VFD	ventilator-free day
WTP	willingness to pay

Plain English summary

The increasing demand for care in an intensive care unit (ICU) currently exceeds supply, leading to a need to explore treatments that may reduce the use of ICU resources and result in increased capacity and improved access to appropriate facilities for critically ill patients. The aim of Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in Acute lung injury to Reduce Pulmonary dysfunction (HARP-2) was to investigate if simvastatin, a drug commonly used to treat high cholesterol, is safe and effective in the treatment of acute lung injury (ALI).

The study was open to patients aged ≥ 16 years who were admitted to specified ICU wards in the UK and who were suffering from ALI. A total of 540 patients were recruited and were randomly allocated to receive either 80 mg of simvastatin or 80 mg of placebo (an identical 'dummy' tablet) for up to 28 days.

To test how simvastatin might work to ease the patient's condition, blood and urine samples were taken to determine the ways in which lung injury develops and to examine how long patients needed assistance with their breathing on a ventilator and how quickly they recovered. Patients were contacted at 3, 6 and 12 months after discharge to fill in a questionnaire to measure the residual effects of the illness on their lives.

The study found that simvastatin was relatively safe with an increase in adverse events but no increase in serious adverse events. The study results show that simvastatin did not significantly improve clinical outcomes for patients and is not of benefit in the management of ALI, but may be used in critically ill patients with a coexisting condition for which a statin is normally prescribed.

Scientific summary

Background

Acute lung injury (ALI) is a common devastating clinical syndrome characterised by life-threatening respiratory failure requiring mechanical ventilation and multiple organ failure, and is a major cause of morbidity and mortality. Acute respiratory distress syndrome (ARDS) is a more severe form of ALI that is characterised by an uncontrolled inflammatory response that results in damage to the alveolar epithelial and endothelial barrier with exudation of protein-rich pulmonary oedema fluid in the alveolar space.

Acute lung injury occurs in response to a variety of insults, such as trauma and severe sepsis. It affects all age groups, has a high mortality rate of up to 30–50% and causes a long-term reduction in the quality of life for survivors. ALI has significant resource implications, as it prolongs intensive care unit (ICU) and hospital stay, and requires rehabilitation in the community. The cost per ICU bed-day exceeds £1400 and delivery of critical care to patients with ALI accounts for a significant proportion of ICU capacity. Only 54% of survivors are able to return to work 12 months after hospital discharge. The high incidence, mortality, long-term consequences and high economic costs mean that ALI is an extremely important problem.

There is a large body of evidence from in vitro and animal studies suggesting that statins may be beneficial in ALI. In summary, statins improve epithelial and endothelial function to reduce alveolar capillary permeability and reduce pulmonary oedema. In addition, they modulate the inflammatory cascade; regulate inflammatory cell recruitment, activation and apoptosis; and reduce cytokine and protease activity. This may improve outcomes, as high levels and persistence of inflammatory mediators in ALI are associated with poor outcome.

Objectives

The aim of this study was to test the hypothesis that treatment with enteral 80 mg of simvastatin once daily compared with placebo for a maximum of 28 days would be of therapeutic value in patients with ALI. The study had two distinct objectives:

- Objective 1: to conduct a prospective randomised, double-blind, placebo-controlled Phase II multitrial of simvastatin for the treatment of ALI.
- Objective 2: to study the biological effect of simvastatin treatment on mechanisms implicated in the development of ARDS.

Methods

We conducted a randomised, allocation-concealed, double-blind, clinical trial of 80 mg of enteral simvastatin or placebo once daily for a maximum of 28 days. The study was approved by a national Research Ethics Committee (REC) and research governance departments at each site in the UK and by the institutional REC at each site in Ireland. The study was also approved by the Medicines and Healthcare Products Regulatory Agency (MHRA) and Irish Medicines Board (IMB). The Northern Ireland Clinical Trials Unit co-ordinated the overall trial, with support from the Health Research Board Galway Clinical Research Facility for centres in Ireland. The study was conducted in accordance with the protocol and the statistical analysis plan and was reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The study design has been published in detail previously.

Daniel F McAuley and John G Laffey vouch for the integrity, accuracy and completeness of the data and analysis and the fidelity of the study to the protocol.

Patients were recruited from adult ICUs in 40 hospitals in the UK and Ireland. Patients' representatives provided written informed consent (assent for sites in Ireland). All surviving patients were subsequently informed about the trial after regaining competence and consent to continue in the trial was obtained.

Patients were eligible if they were intubated and mechanically ventilated and had acute onset of ALI, as defined by the presence of hypoxic respiratory failure ($PaO_2 : FiO_2$ of ≤ 40 kPa from two arterial blood gas tests taken > 1 hour apart); the presence of bilateral infiltrates on chest radiograph consistent with pulmonary oedema; and if there was no clinical evidence of left atrial hypertension or, if measured, a pulmonary arterial occlusion pressure (PAOP) of ≤ 18 mmHg. If a patient had a PAOP of > 18 mmHg, then the other criteria must have persisted for > 12 hours after the PAOP had declined to < 18 mmHg, and still be within the 48-hour enrolment window.

The exclusion criteria were:

- aged < 16 years
- presence of ALI for > 48 hours
- pregnancy
- creatine kinase (CK) levels of > 10 times the upper limit of the normal range
- alanine transaminase (ALT) and/or aspartate aminotransferase (AST) levels of > 8 times the upper limit of the normal range
- receiving ongoing and sustained treatment with concomitant drugs
- severe renal impairment and not receiving renal replacement therapy
- severe liver disease
- current or recent treatment with a statin (within 2 weeks)
- physician decision that a statin is required for proven indication
- contraindication to enteral drug administration
- domiciliary mechanical ventilation except for continuous positive airway pressure/bilevel positive airway pressure used for sleep-disordered breathing
- known participation in another clinical trial of an investigational medicinal product within the previous 30 days
- consent declined
- treatment withdrawal imminent within 24 hours
- non-English speaking without the presence of an interpreter.

On examination of the screening data submitted by sites, it became apparent that the inclusion of clarithromycin and erythromycin in the exclusion criteria had a significant effect on recruitment, with 10% of patients excluded because they were receiving these drugs. To address this situation, a substantial amendment was submitted and authorised in August 2011, allowing the removal of clarithromycin and erythromycin from the exclusion criteria. A further amendment was also approved to increase the eligibility level of ALT and/or AST from more than five times the upper limit of normal to more than eight times the upper limit of the normal range; this amendment was approved in March 2012. Both of these amendments allowed for a significant improvement in recruitment.

A total of 40 mg of simvastatin or identical placebo (95% lactose) tablets were packaged identically and identified only by the unique trial identifier. A computer-generated randomisation sequence was used. Patients were randomised in a 1 : 1 ratio using an automated centralised 24-hour telephone or web-based randomisation service (Centre for Healthcare Randomised Trials, University of Aberdeen, UK). Randomisation was by permuted block stratified by site and by vasopressor requirement (defined as any inotropic requirement except dopamine < 6 µg per kg per minute).

Patients received 80 mg of simvastatin once daily (as two 40-mg tablets) or two identical placebo tablets administered enterally via a feeding tube or orally for up to 28 days. The first dose of study drug was administered as soon as possible, ideally within 4 hours of randomisation, and subsequent doses were given each morning starting on the following calendar day.

The trial drug was terminated if any one of the following conditions was met, prior to the maximum treatment period (28 days from randomisation): study drug-related AE; CK level of > 10 times the upper limit of normal; ALT/AST level of > 8 times the upper limit of normal; development of a clinical condition requiring immediate treatment with a statin; discharge from critical care environment; death; discontinuation of active medical treatment; patient or relative request for withdrawal of patient from the study; decision by the attending clinician that the study drug should be discontinued on safety grounds.

Patient health-related quality of life and resource use was measured by the EuroQol-5 Dimensions, three-level version questionnaire, completed at hospital discharge, and a follow-up questionnaire that was posted out to all patients 3, 6 and 12 months after the date of patient randomisation.

Neutrophil activation was measured by plasma matrix metalloproteinase (MMP)-8. Systemic inflammation and acute phase responses were measured by interleukin 6 (IL-6), C-reactive protein (CRP) and 25-hydroxyvitamin D (vitamin D). Alveolar epithelial and endothelial activation/injury were measured by plasma receptor for advanced glycation end-products (RAGE) and angiopoietin 2 (Ang2) levels respectively. Plasma concentrations were measured at recruitment (baseline) and day 3 (except vitamin D, which was measured to day 14). Plasma concentrations of MMP-8, IL-6, Ang2 and RAGE were measured by enzyme-linked immunosorbent assay. CRP was measured by immunoturbidimetric assay performed by Randox Laboratories (Crumlin, Northern Ireland). Plasma vitamin D was measured by liquid chromatography mass spectrometry by colleagues in the laboratory of Barbara Obemayer-Pietsch, Heidelberg, Germany.

Results

Patients were recruited from 21 December 2010 until 13 March 2014. Out of the 5926 patients who were assessed for eligibility, 540 (9%) underwent randomisation. Four patients who did not fulfil the eligibility criteria were randomised in each group and are included in the analysis. Five patients allocated to the simvastatin group and three patients in the placebo group did not receive study drug. One patient in the simvastatin group was lost to follow-up. No data on the primary outcome were available for one patient in the simvastatin group and two patients in the placebo group.

The baseline characteristics of the patients at randomisation were similar in the two study groups. The main causes of ARDS were pneumonia and sepsis.

Patients received study drug for a mean of 10.2 days [standard deviation (SD) 7.1 days] in the simvastatin group and 11 days (SD 7.9 days) in the placebo group ($p = 0.23$). The most common reasons for discontinuation of study drug were discharge from critical care, death and a study drug-related adverse event (AE). Five patients allocated to the simvastatin group and three patients allocated to the placebo group received treatment with non-trial statins.

Outcomes

The number of ventilator-free days (VFDs) was not significantly different between the study groups [12.6 days (SD 9.9 days) in the simvastatin group and 11.5 days (SD 10.4 days) in the placebo group; $p = 0.21$]. There was no significant difference in the number of VFDs after adjusting for the baseline $PaO_2 : FiO_2$ ratio {mean difference 1.4 [95% confidence interval (CI) –0.3 to 3.2; $p = 0.10$]}.

There was a larger improvement in the oxygenation index (OI) from baseline in the simvastatin group at day 3 but there were no significant differences in the change in OI or sequential organ failure assessment (SOFA) score from baseline between the groups. There was no significant difference in the number of non-pulmonary organ failure-free days between the groups. There was also no significant difference between the study groups in 28-day mortality.

Mortality at critical care discharge, hospital discharge or 12 months post randomisation were also not significantly different between the groups. For survivors only, the mean duration of ICU stay was 13.9 days (SD 14.4 days) in the simvastatin group and 14.4 days (SD 13.3 days) in the placebo group ($p = 0.71$); and the mean duration of hospital stay was 37.7 days (SD 64.5 days) and 35.4 days (SD 311 days), respectively ($p = 0.66$). There was no significant difference in the probability of breathing without assistance to day 28 or survival. Hazard ratios reported are for the comparison of the placebo group with the simvastatin group.

Prior subgroup analyses did not suggest that the effects of simvastatin were modified by any of the variables investigated. There was no statistically significant interaction between treatment and age ($p = 0.62$), vasopressor requirement ($p = 0.17$) or presence of sepsis ($p = 0.50$).

Simvastatin had no effect on systemic markers of neutrophil activation, systemic inflammation and acute phase response, nor on markers of alveolar epithelial or endothelial activation and injury. Stratifying patients according to their relative baseline degree of cell-specific injury or systemic inflammation did not identify a subgroup that benefited from simvastatin in terms of improving VFDs or 28-day mortality.

Overall AEs related to the study drug were significantly more common in the simvastatin group. The majority were related to elevated levels of CK and hepatic transaminases. Serious adverse events (SAEs) (other than those reported as trial outcomes, e.g. death) were reported in 25 patients (11 patients in the simvastatin group and 14 patients in the placebo group). In total, 28 SAEs were reported (12 in the simvastatin group and 16 in the placebo group), with one patient in the simvastatin group having two SAEs and two patients in the placebo group each having two SAEs.

The return rate of the follow-up questionnaires was 60% for the 3-month questionnaires, 59% for the 6-month questionnaires and 53% for the 12-month questionnaires.

Simvastatin was cost-effective at 1 year compared with placebo for the treatment of ARDS, and was associated with both a small quality-adjusted life-year (QALY) gain (0.064, 95% CI 0.002 to 0.127) and a cost saving (£3601, 95% CI –£8061.10 to £859.28).

Conclusion

Simvastatin, although safe and generally well tolerated, did not increase the number of VFDs or improve mortality in patients with ARDS. However, it was found to be highly cost-effective at 1 year compared with placebo, and was associated with both a small QALY gain and a cost saving.

However, given the small impact on QALYs, as well as the health economics analysis being a secondary outcome of this study, and that the assumptions underpinning the economic benefit are based on the analysis of a subgroup of responders, there is insufficient evidence to support the treatment of patients with ARDS with simvastatin in the NHS. There is a need to confirm if ARDS endotypes that are more likely to benefit from targeted treatment with simvastatin exist. The potential role of simvastatin in the prevention of ARDS in patients at a high risk of developing ARDS has not yet been evaluated.

Trial registration

This trial is registered as ISRCTN88244364.

Funding

This project was funded by the Efficacy and Mechanism Evaluation programme, a Medical Research Council and National Institute for Health Research partnership. This study was also funded in the Republic of Ireland by the Health Research Board (HRA_POR-2010-131). In addition, the Health and Social Care Research and Development division of the Public Health Agency in Northern Ireland, the Intensive Care Society of Ireland and Randomized Exploratory Clinical Trial to Evaluate the Safety and Effectiveness of Stem Cell Product in Alcoholic Liver Cirrhosis Patient (REVIVE) provided additional funding.

Chapter 1 Introduction

Description of acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is a condition characterised by a failure of pulmonary oxygen exchange due to increased alveolar–capillary permeability and resultant pulmonary oedema. It can be caused by primary lung conditions such as aspiration, pneumonitis or can arise as a complication of non-pulmonary conditions such as severe sepsis. The syndrome was first described by Ashbaugh *et al.*[1] in 1967 in a group of 12 patients with acute onset on dyspnoea, tachypnoea, refactory hypoxaemia, reduced pulmonary compliance and diffuse alveolar shadowing on their chest radiographs. All the patients required positive and expiratory pressure to maintain arterial oxygenation. The term 'adult respiratory distress syndrome' was initially used to describe the condition[2] but it was subsequently renamed ARDS because it may also occur in children.[3] The current definition arose from the American–European Consensus Conference in 1994[4] and recognised two grades of the disease, separated by the degree of hypoxaemia. ARDS was reserved for the more severe grade, with acute lung injury (ALI) being used as the overall term. The definition of ALI/ARDS requires:

- acute onset of bilateral infiltrates on chest radiographs
- pulmonary arterial occlusion pressure (PAOP) of < 18 mmHg (if measured) or absence of clinical signs of left atrial hypertension
- ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen ($PaO_2 : FiO_2$) of < 200 mmHg (26.7 kPa) for ARDS, or $PaO_2 : FiO_2$ of < 300 mmHg (40 kPa) for ALI.

Incidence and burden of acute lung injury

Acute lung injury is a major cause of morbidity and mortality. It affects all age groups, has a high mortality rate of up to 30–50%[5–7] and causes a long-term reduction in quality of life for survivors.[7] ALI has significant resource implications, prolonging intensive care unit (ICU) and hospital stay, and requiring rehabilitation in the community.[8] The cost per ICU bed-day exceeds £1400 and delivery of critical care to patients with ALI accounts for a significant proportion of ICU capacity. Only 54% of survivors are able to return to work 12 months after hospital discharge.[9] The high incidence, mortality, long-term consequences and high economic costs mean that ALI is an extremely important problem.

Rationale for the trial

Prior evidence

There was a large body of evidence from in vitro and animal studies suggesting that statins might be beneficial in ALI.[10] In summary, statins improved epithelial and endothelial function to reduce alveolar capillary permeability and reduced pulmonary oedema. In addition, they modulated the inflammatory cascade; regulated inflammatory cell recruitment, activation and apoptosis; and reduced cytokine and protease activity. This suggested that statins might improve outcomes, as high levels and persistence of inflammatory mediators in ALI are associated with poor outcome.[11]

Lack of published randomised controlled trials of statins in acute lung injury

There was a lack of published randomised controlled trials (RCTs) of statins in ALI. We conducted a systematic review, searched registries of ongoing clinical trials and contacted national and international experts in ALI. The National Institutes of Health had conducted a Phase III multicentre trial involving statins, but this involved rosuvastatin (Crestor, AstraZeneca UK Ltd) compared with placebo for up to 28 days in

patients with sepsis-induced respiratory failure in the USA.[12] Our trial examined simvastatin and investigated ALI due to all aetiologies, as well as studying the potential mechanism of action by which statins act. In addition, unlike the US trial, an economic evaluation was undertaken in this study.

Observational studies support a clinical trial of a statin in acute lung injury

Acute lung injury is the most common complication of severe sepsis.[13] In patients with sepsis, most observational studies[14–17] suggest that statins are associated with better outcomes, as measured by morbidity and mortality. Similarly, most observational studies[18–20] have suggested a beneficial effect of statins in patients with pneumonia, supporting a potential role for statins in modulating pulmonary inflammation.

The Irish Critical Care Trials Group (ICCTG) has undertaken a prospective observational study in patients with ALI, which found that mortality was lower in patients receiving statins during their ICU stay. After adjusting for plateau pressure, severity of illness and other relevant covariates in a multiple logistic regression model, patients receiving statins had a much lower probability of death, although this failed to reach significance [odds ratio (OR) 0.27, 95% confidence interval (CI) 0.06 to 1.21; $p = 0.09$].[21] Similarly, in a retrospective study, statin usage in patients with ALI was associated with increased ventilator-free days (VFDs) and reduced mortality, although again this was not significant.[22] These observational studies were not powered to examine the effect of statins on mortality.

It was not clear if the association with better outcomes in these studies was due to statins as opposed to statins representing a surrogate marker for improved access to health care. Moreover, these studies did not demonstrate whether or not beneficial effects would occur when statins were commenced after the onset of ALI. Although these data suggested that statins may have a potentially beneficial pharmacological treatment in ALI, a trial powered for important clinical outcomes was required.

Simvastatin reduces lipopolysaccharide-induced pulmonary and systemic inflammation in humans

We had conducted a study to examine if simvastatin modulates pathogenic mechanisms important in the development of lung injury in a model of acute lung inflammation induced by inhaled lipopolysaccharide (LPS) in healthy human volunteers.[23] In this double-blind, placebo-controlled study, participants were randomised to the simvastatin group or the placebo orally for 4 days prior to LPS inhalation group. Pre treatment with simvastatin reduced mediators of early ALI in bronchoalveolar lavage fluid including tumour necrosis factor alpha (TNF-α), neutrophil myeloperoxidase and protease release as measured by neutrophil elastase and matrix metalloproteinase (MMP)-7, -8 and -9. Furthermore, there was a significant reduction in systemic inflammation as measured by plasma C-reactive protein (CRP) levels. These effects were associated with reduced nuclear factor kappa B translocation. These novel findings provided the first proof of the principle that simvastatin has important anti-inflammatory effects in vivo in humans who are challenged with aerosolised endotoxin. These mechanistic findings were supported by a randomised placebo-controlled study that found 80 mg of simvastatin for 4 days reduced systemic cytokine responses induced by low-dose intravenous LPS in healthy subjects.[24] Finally, a randomised placebo-controlled study in patients with acute bacterial infection found that simvastatin, commenced prior to the development of sepsis-induced organ dysfunction, also reduced the levels of systemic inflammatory cytokines [TNF-α and interleukin 6 (IL-6)].[25]

Proof of concept that simvastatin improves pulmonary and non-pulmonary organ dysfunction, reduces inflammation and is well tolerated in patients with acute lung injury

We had completed a single-centre, randomised, double-blind, placebo-controlled Phase II study of simvastatin (80 mg for up to 14 days) in 60 patients with ALI. By day 14 there was a trend to improvement in pulmonary dysfunction, as measured by the oxygenation index (OI), respiratory system compliance and lung injury score in the simvastatin-treated group. Non-pulmonary organ dysfunction, as measured by the sequential organ failure assessment (SOFA) score was significantly lower in the simvastatin-treated group,

with improvements in cardiovascular, renal and coagulation function. There was no difference in outcome for patients with sepsis- or non-sepsis-related ALI. Importantly, 80 mg of simvastatin was well tolerated with no increase in adverse events (AEs). In addition, we found that, unlike placebo, simvastatin decreased pulmonary IL-8 2.5-fold by day 3, with a trend to a decrease in IL-6 2.9-fold. In addition, at day 14 plasma CRP was lower with a trend to reduced plasma IL-6 in the simvastatin-treated group.[26]

Together these results reflected the beneficial effects seen in previous in vitro and animal studies.[10] The study described above was not designed or powered to show an effect of simvastatin on VFDs or mortality. However, pulmonary and non-pulmonary organ dysfunction, as well as high levels of inflammatory cytokines, were associated with fewer VFDs and higher ICU mortality, which suggested that simvastatin might lead to improved clinical outcomes.

The findings above were supported by two small prospective randomised controlled studies involving the acute use of statins in patients with sepsis and pneumonia.[27,28] Choi *et al.*[27] studied 10 mg of atorvastatin (Lipitor®, Pfizer) given once daily in 74 patients with sepsis and pneumonia. Hospital mortality was reduced in the atorvastatin group compared with placebo, although this failed to reach significance (47% vs. 53%; $p = 0.06$). Similarly, Gonzalez *et al.*[28] conducted a study of 80 mg of simvastatin given once daily or placebo for 14 days in 40 patients with sepsis and found that simvastatin decreased the length of hospital stay.

Rationale for statins in acute lung injury

Statins have been proven to be a well-tolerated class of drugs. An improved mortality rate and no AEs have been reported in observational studies in critically ill patients with sepsis who were receiving statins.[15–21] Importantly, no toxicity was reported when statins were continued throughout the ICU course.

A dose of 80 mg of simvastatin is within the licensed therapeutic range for the treatment of hypercholesterolaemia in the UK. Although a different patient population, there is evidence regarding the safety of 80 mg of simvastatin in patients with cardiovascular disease. In a study in which 2265 patients following an acute coronary syndrome were randomised to receive 80 mg of simvastatin, myopathy [creatine kinase (CK) levels of > 10 times the upper limit of normal associated with muscle symptoms] occurred in only 0.4% of participants and rhabdomyolysis (CK levels of > 10,000 units/l with or without muscle symptoms) occurred in 0.13% of participants receiving 80 mg of simvastatin.[29] Importantly in this study, follow-up was only at months 1, 4 and 8 and every 4 months thereafter for up to 24 months until trial completion. In a further study in which 6031 patients with a history of a previous myocardial infarction were randomised to receive 80 mg of simvastatin, myopathy occurred in 0.9% and rhabdomyolysis in 0.18% of participants.[30] In this study, participants were seen for follow-up only at 2, 4, 8 and 12 months, and then at 6-month intervals with a median follow-up of 6 years. It is important to emphasis the maximum treatment period with 80 mg of simvastatin in this study was 28 days with safety monitoring (CK and liver transaminases) at days 3, 7, 14, 21 and 28.

The data from our proof-of-concept study reassuringly found that 80 mg of simvastatin was well tolerated and not associated with increased AEs compared with placebo. There was no difference in CK levels or numbers of patients with a CK level of > 10 times the upper limit of normal between the groups. There were no differences in creatinine levels between the groups. Reassuringly, there was a trend towards a lower incidence of renal replacement therapy at day 14 in the simvastatin-treated group. Liver transaminases [alanine transaminase (ALT) and aspartate aminotransferase (AST)] were commonly elevated and, although not significant, this was more common in the placebo-treated group. There were no differences in AEs or serious adverse events (SAEs) between the groups. No drug-related SAEs occurred during the study.[26]

Rationale for choice of simvastatin

The diverse effects of statins appeared to represent a class effect. As outlined above, in both in vitro and animal experiments statins showed consistent effects regardless of the choice of statin. In addition, retrospective and prospective human studies have included multiple statins and shown beneficial effects. However, as the only statin with proof-of-concept efficacy and safety data in ALI, simvastatin was investigated in this study.

Rationale for simvastatin 28-day duration of treatment

The decision to examine treatment for up to 28 days was based on (1) data from our proof-of-concept study that demonstrated ongoing clinical improvement to day 14,[26] (2) data showing that the upper interquartile range for duration of ICU stay in patients with ALI/ARDS is 14–18 days[5,7,9] and (3) observational trials that showed benefit with no reported toxicity when statins were continued throughout the ICU stay.[21,22]

Rationale for 80 mg of simvastatin dosage

Although there were a large number of data suggesting that statins might be beneficial in animal models of ALI, only a single animal study compared two doses of simvastatin (5 mg/kg or 20 mg/kg given intraperitoneally 24 hours before and concomitantly with LPS to induce lung injury) and only the higher dose was effective in attenuating lung injury.[31]

Importantly, a retrospective observational study of statin usage in patients with sepsis found a greater mortality benefit in patients who were receiving a higher dose of statin.[32]

A dose of 80 mg of simvastatin is the only dose with proof-of-concept data and is well tolerated in ALI. Therefore, 80 mg of simvastatin compared with placebo once daily was investigated in this study.

Although it is acknowledged that the risk of adverse side effects is dose related, on the basis of available evidence 80 mg of simvastatin is safe, particularly given that the duration of treatment was only up to 28 days and these patients were intensively monitored.

There are no effective pharmacological therapies for acute lung injury

The Cochrane systematic review of pharmacological treatments that included 22 studies of 14 different drugs concluded that ‘effective pharmacotherapy for ALI is extremely limited, with insufficient evidence to support any specific intervention’.[33]

The National Heart, Lung and Blood Institute working group considered the future research directions in ALI in 2002 and concluded that clinical trials underpinned by mechanistic investigations were essential to develop new therapies for ALI.[34]

Chapter 2 Methods

Trial summary

Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in Acute lung injury to Reduce Pulmonary dysfunction (HARP-2) was a multicentre, randomised, allocation-concealed, double-blind, placebo-controlled clinical trial of 80 mg of enteral simvastatin or placebo once daily for a maximum of 28 days. Patients were recruited from adult general ICUs in 40 hospitals throughout the UK and Ireland. The study was approved by the Office for Research Ethics Committees Northern Ireland (ORECNI) (10/NIR02/36) and research governance departments at each site in the UK and by the Clinical Research Ethics Committee (CREC) at each site in Ireland (8/10). The study was approved by the Medicines and Healthcare Products Regulatory Agency (MHRA) (32485/0020/001-0001) and Irish Medicines Board (IMB) (CT900/495/1).

The Northern Ireland Clinical Trials Unit (NICTU) co-ordinated the overall trial, with support from the Health Research Board (HRB) Galway Clinical Research Facility for centres in Ireland.

The study was conducted in accordance with the protocol and the statistical analysis plan and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[35]

The primary outcome measure was VFDs up to day 28 (defined as the number of days from the time of initiating unassisted breathing to day 28 after randomisation), with follow-up for mortality and quality of life to 12 months. The target sample size was 540 patients. The trial protocol and the results to 28 days have been published.[36,37]

Objectives

The aim was to test the hypothesis that treatment with 80 mg of enteral simvastatin once daily for a maximum of 28 days was of therapeutic value in patients with ALI. The study had two distinct objectives:

- Objective 1: to conduct a prospective randomised, double-blind, placebo-controlled Phase II multitrial of simvastatin for the treatment of ALI.
- Objective 2: to study the biological effect of simvastatin treatment on mechanisms implicated in the development of ARDS.

Outcome measures

Primary outcome measure

The primary outcome measure was VFDs to day 28, defined as the number of days from the time of initiating unassisted breathing to day 28 after randomisation, assuming survival for at least 2 consecutive calendar days after initiating unassisted breathing and continued unassisted breathing to day 28. If a patient returned to assisted breathing and subsequently achieved unassisted breathing to day 28, VFDs were counted from the end of the last period of assisted breathing to day 28. A period of assisted breathing lasting < 24 hours and for the purpose of a surgical procedure was not counted against the VFD calculation. If a patient was receiving assisted breathing at day 27 or died prior to day 28, VFDs were counted as zero. Patients transferred to another hospital or other health-care facility were followed to day 28 to assess this end point.

In keeping with previous trials,[38,39] unassisted breathing was defined as:

- extubated with supplemental oxygen or room air or
- open T-tube breathing or
- tracheostomy mask breathing or
- continuous positive airway pressure of ≤ 5 cm H_2O without pressure support.

Patients receiving pressure support via non-invasive ventilation were defined as receiving assisted ventilation.

Secondary outcome measures

The secondary outcomes for this clinical trial included clinical outcomes, safety, biological mechanisms and data for the economic evaluation.

Clinical outcomes

- Change in OI from baseline to day 3, 7, 14 and 28.
- Change in SOFA score from baseline to day 3, 7, 14 and 28.
- Non-pulmonary organ failure-free days (defined as the number of days in the first 28 days after randomisation that the patient has none of the following: cardiovascular support, renal support, liver support or neurological support).
- All-cause mortality 28 days post randomisation.
- Mortality at (first) discharge from critical care.
- Mortality at (first) discharge from hospital.
- Mortality at 12 months post randomisation.

Safety outcomes

- A CK level of > 10 times the upper limit of normal (measured on days 1, 3, 7, 14, 21 and 28).
- ALT/AST level of > 8 times the upper limit of normal (measured on days 1, 3, 7, 14, 21 and 28).
- Need for renal replacement therapy in patients with CK levels elevated > 10-fold.
- The SAEs and occurrence of suspected unexpected serious adverse reactions (SUSARs), as defined in *Chapter 3, Safety outcomes*.

Biological mechanisms

The effects of statins on biological mechanisms known to be important in ARDS were investigated as below:

- Neutrophil activation as measured by plasma MMP-8 concentration.
- Plasma acute phase inflammatory response as measured by CRP, IL-6 and vitamin D concentration.
- Alveolar epithelial injury as measured by plasma receptor for advanced glycation end-products (RAGE) concentration and alveolar endothelial injury as measured by plasma angiopoietin 2 (Ang2) concentration.

Data for economic evaluation

- Health-related quality of life (HRQoL)
  - EuroQol-5 Dimensions (EQ-5D) at discharge, 3, 6 and 12 months post randomisation.
- Resource use
  - length of ICU stay (level 3 care)
  - length of high-dependency unit (HDU) stay (level 2 care).
  - length of hospital stay
  - health service contacts up to 12 months post randomisation.

Inclusion/exclusion criteria

Inclusion criteria

- Patients receiving invasive mechanical ventilation.
- Patient with ALI[4] as defined by:
    - acute onset of hypoxic respiratory failure ($PaO_2 : FiO_2$ of ≤ 40 kPa from two arterial blood gas tests > 1 hour apart)
    - bilateral infiltrates on chest radiograph consistent with pulmonary oedema
    - no clinical evidence of left atrial hypertension or, if measured, a PAOP of ≤ 18 mmHg. If a patient has a PAOP of > 18 mmHg, then the other criteria must have persisted for > 12 hours after the PAOP had declined to < 18 mmHg, and still be within the 48-hour enrolment window.

Acute onset was defined as follows: the duration of the hypoxia criterion (1) and the chest radiograph criterion (2) must have been < 28 days at the time of randomisation.

Infiltrates considered 'consistent with pulmonary oedema' included any patchy or diffuse infiltrates not fully explained by mass, atelectasis, or effusion or opacities known to be chronic (> 28 days). The findings of vascular redistribution, indistinct vessels and indistinct cardiac borders were not considered 'consistent with pulmonary oedema'.

All ALI criteria (under the second bullet point above) must have occurred within the same 24-hour period. The time of onset of ALI was when the last ALI criterion was met. Patients were enrolled within 48 hours of ALI onset.

Exclusion criteria

- Aged < 16 years.
- There had been > 48 hours since the onset of ALI.
- Patient was known to be pregnant.
- A CK level of > 10 times the upper limit of the normal range.*
- Transaminase levels of > 8 times the upper limit of the normal range.*
- Patients receiving ongoing and sustained treatment with any of the following: itraconazole, ketoconazole, human immunodeficiency virus (HIV) protease inhibitors, nefazodone (Dutonin, Bristol-Myers Squibb), ciclosporin, amiodarone, verapamil or diltiazem.
- Patients with severe renal impairment (estimated creatinine clearance of < 30 ml/minute) not receiving renal replacement therapy.
- Severe liver disease (Child–Pugh score of > 12).
- Current or recent treatment (within 2 weeks) with statins.
- Physician decision that a statin was required for proven indication.
- Contraindication to enteral drug administration (e.g. patients with mechanical bowel obstruction). Patients with high gastric aspirates due to an ileus were not excluded.
- Domiciliary mechanical ventilation except for continuous positive airway pressure/bilevel positive airway pressure used for sleep-disordered breathing.
- Known participation in other investigational medicinal product trials within 30 days.
- Consent declined.
- Treatment withdrawal imminent within 24 hours.
- Non-English-speaking patients or those who did not adequately understand verbal or written information unless an interpreter was available.

*If CK, ALT and AST values were not available as part of routine care, a blood sample was obtained after informed consent but before randomisation.

The CK, ALT and AST values could be obtained up to 72 hours prior to randomisation.

The following amendments relating to eligibility were made during the study.

- Protocol version 2.0: the exclusion criteria were amended to allow patients receiving low-dose erythromycin as a prokinetic to be included.
- Protocol version 3.0: concomitant use of clarithromycin and erythromycin and domicilliary ventilation for sleep-disordered breathing were removed as exclusion criteria.
- Protocol version 4.0: level of ALT and AST for eligibility and discontinuation of study drug was changed from five times the upper limit of normal to eight times the upper limit of normal.

Consent

The study was conducted in accordance with the ethics principles that have their origin in the Declaration of Helsinki. Eligible patients were included in the trial only after written informed consent was obtained. Informed consent was obtained prior to conducting any trial-specific procedures and the process for obtaining informed consent was documented in the patient's medical records (source documents that were reviewed at the time of on-site monitoring visits).

Informed consent procedure for the UK

Informed consent forms approved by the Research Ethics Committee (REC) were provided to each trial site. The principal investigator (PI) was responsible for ensuring that informed consent for trial participation was given by each patient or a legal representative. This required that the informed consent form was signed and personally dated by the patient or by the patient's legally acceptable representative. An appropriately trained doctor or nurse took consent. If no consent was given, then the patient was not randomised into the trial.

The incapacitating nature of the condition precluded obtaining prospective informed consent from participants. In this situation, informed consent was sought from a personal legal representative (PerLR) or professional legal representative (ProfLR) when a PerLR was not available.

Personal legal representative consent: UK

Informed consent was sought from the patient's PerLR, who was a relative, partner or close friend. The PerLR was informed about the trial by the responsible clinician or a member of the research team and they were provided with a copy of the covering statement for the PerLR with an attached patient information sheet (PIS) and asked to give an opinion on whether or not the patient would object to taking part in such medical research. If the PerLR decided that the patient would have no objection to participating in the trial, then they were asked to sign two copies of the PerLR consent form, which were then countersigned by the person taking consent. A copy of the signed informed consent form was placed in the patients' medical records, while the originals were retained by the PerLR and by the PI in the investigator site file (ISF).

Professional legal representative consent: UK

If the patient was unable to give informed consent and no PerLR was available, a doctor who was not connected with the conduct of the trial acted as a ProfLR. The doctor was informed about the trial by the responsible clinician or a member of the research team and given a copy of the PIS. If the doctor decided that the patient was suitable for entry into the trial, they were asked to sign two copies of the ProfLR consent form. A copy of the signed informed consent form was placed in the patients' medical records, while the originals were retained by the doctor ProfLR and by the PI in the ISF.

Retrospective patient consent: UK

Patients were informed of their participation in the trial by the responsible clinician or a member of the research team once they regained capacity to understand the details of the trial. The responsible clinician or a member of the research team discussed the study with the patient and the patient was given a copy of the PIS to keep. The patient was asked for consent to participate in the trial and to sign two copies of the consent to continue form, which were then countersigned by the person taking consent. A copy of the signed consent form was placed in the patient's medical records while the originals were retained by the patient and by the PI in the ISF. When consent to continue was not obtained, consent from the legal representative remained valid. If the patient refused consent, data collected about the patient were not entered into the analysis.

Informed consent/assent procedure for Ireland

Informed consent/assent forms approved by the CREC were provided to each trial site. The PI was responsible for ensuring that informed consent/assent for trial participation was given by each patient or their representative respectively. This required that the informed consent/assent form be signed and personally dated by the patient or by their representative. An appropriately trained doctor or nurse took consent. If no assent was given, the patient was not randomised into the trial.

The incapacitating nature of the condition precluded obtaining prospective informed consent from participants. In this situation, informed assent was sought from the patient's representative or from a professional representative if no suitable representative was available.

Patient representative assent: Ireland

Informed assent was sought from the patient's representative who was a relative, partner or close friend. The patient representative was informed about the trial by the responsible clinician or a member of the research team and they were provided with a copy of the covering statement for the representative with an attached PIS and asked to give an opinion on whether or not the patient would object to taking part in such medical research. If the patient representative decided that the patient would have no objection to participating in the trial they were asked to sign two copies of the patient representative assent form, which was then countersigned by the person taking consent. A copy of the signed informed assent form was placed in the patient's medical records, while the originals were retained by the patient representative and by the PI in the ISF.

Professional representative assent: Ireland

If the patient was unable to give informed consent and no patient representative was available, a doctor who was not connected with the conduct of the trial acted as a professional representative. The doctor was informed about the trial by the responsible clinician or a member of the research team and given a copy of the PIS. If the doctor decided that the patient was suitable for entry into the trial, they were asked to sign two copies of the professional representative assent form. A copy of the signed informed assent form was placed in the patient's medical records, while the originals were retained by the professional representative and by the PI in the ISF.

Retrospective patient consent: Ireland

Patients were informed of their participation in the trial by the responsible clinician or a member of the research team once they regained the capacity to understand the details of the trial. The responsible clinician or a member of the research team discussed the study with the patient and the patient was given a copy of the PIS to keep. The patient was asked for consent to participate in the trial and to sign two copies of the consent to continue form, which was then countersigned by the person taking consent. A copy of the signed consent form was placed in the patient's medical records while the originals were retained by the patient and by the PI in the ISF. When consent to continue was not obtained, consent from the patient or professional representative remained valid. If the patient refused consent, data collected about the patient were not entered into the analysis.

Withdrawal of consent: UK and Ireland

Patients could withdraw or be withdrawn (by PerLR or ProfLR) from the trial at any time without prejudice. Data recorded up to the point of withdrawal were included in the trial analysis, unless consent/assent to use the patient's data had also been withdrawn. If a patient or legal representative requested termination of the trial drug during the treatment period, the drug was stopped but the patient continued to be followed up as part of the trial. If a patient or a PerLR withdrew consent/assent during trial treatment, the trial drug was stopped but permission was sought to access medical records for data related to the trial. If a patient or PerLR wished to withdraw from the trial after completion of trial treatment, permission to access medical records for trial data was sought.

Randomisation

After informed consent, patients were randomised using an automated 24-hour telephone randomisation service provided by the Centre for Healthcare Randomised Trials (University of Aberdeen, UK). Randomisation was stratified by site and by vasopressor requirement (defined as any inotropic requirement except dopamine of < 6 µg per kg per minute). The randomisation service used a computer-generated random number sequence and allocated a numbered treatment pack to each patient.

Each site participating in the study had a unique site number that had to be entered when using the randomisation system. The randomisation service required confirmation that the patient fulfilled the trial entry criteria and requested the data required for stratification. Using the computer-generated random number sequence, the randomisation service allocated a unique trial identification number in accordance with the study randomisation schedule prepared prior to the start of the trial. This identification number was used throughout the trial for purposes of patient identification. The clinician then recorded the unique patient identification number on to the prescription, which was then handed to the pharmacy who handed over the matching pre-numbered drug pack. The randomisation service confirmed randomisation details by e-mail to the Clinical Trials Unit (CTU), chief investigator and to the study site pharmacy.

Trial treatment

The trial drug packs contained 70 × 40-mg tablets of either simvastatin or placebo. This allowed for 80 mg (2 × 40-mg tablets) to be given daily up to a maximum of 28 days with 7 days of study drug over requirement to allow for spillage or spoilage.

Drug pack preparation and supply

Patient drug packs were prepared by Victoria Pharmaceuticals, Belfast, UK. A dose of 40 mg of simvastatin or identical placebo tablets were packaged in a white opaque high-density polyethylene plastic container, which was sealed with a tamper-evident seal and labelled in compliance with applicable regulatory requirements. All trial drugs were packaged identically and identified only by the unique trial identifier.

Drug packs were stored by Victoria Pharmaceuticals and dispatched by them to participating hospital pharmacies under the instruction of the trial manager who monitored recruitment at participating sites. Hospital pharmacies ensured that all study drugs were stored in a secured area that was separate from normal hospital stock under the manufacturer's recommended storage conditions.

As several sites experienced problems with accessing the pharmacy out of office hours, advice was sought from MHRA on storing the study drug on ICUs. MHRA advised that this was acceptable on the following conditions being met: this must be acceptable to the site pharmacist, the drugs must be received in to the site pharmacy and dispensed out to the ICU, accountability logs must record this action, and study drugs must be kept in a secure temperature-monitored environment. Several sites stored the study drug on the ICU and the location within the ICU was checked at monitoring visits.

Administration of trial drug

The first dose of study drug was administered as soon as possible, ideally within 4 hours of randomisation and subsequent doses were given each morning starting on the following calendar day. If, for any reason, a dose was not administered at the intended time, clinicians were advised to administer it subsequently but not > 12 hours after the intended time of administration. The study drug was most commonly administered via a nasogastric tube; however, if the patient was extubated and receiving oral intake prior to critical care discharge, then the study drug could be administered orally.

If patients received more than a single bolus of amiodarone after randomisation, then the dose was reduced to 40 mg on alternate dates (i.e. one tablet on alternate days for the duration of the treatment period).

Trial drug termination criteria

The trial drug was terminated if any one of the following conditions was met, prior to the maximum treatment period (28 days from randomisation):

- study drug-related AE
    - CK level of > 10 times the upper limit of normal
    - ALT/AST level of > 8 times the upper limit of normal
- development of a clinical condition requiring immediate treatment with a statin
- discharge from critical care environment
- death
- discontinuation of active medical treatment
- patient or relative request for withdrawal of patient from the study
- decision by the attending clinician that the study drug should be discontinued on safety grounds.

Clinical management of patients in the trial

Patients involved in the HARP-2 trial were managed according to best practice established locally on each unit.

Participating ICUs were encouraged to use low tidal volume ventilation at 6–8 ml per kg of predicted body weight and to maintain plateau pressure of < 30 cm H_2O. All other treatment was determined by the patients' physicians.

Serious adverse events and suspected unexpected serious adverse reactions

Assessment of causality

Each AE was clinically assessed for causality based on the information available (i.e. the relationship of the AE to the study drug). For the purposes of this trial, the causality was assessed using the categories presented below. Drug-related AEs were defined as those considered by the PI to have a possible, probable or definite relationship to the study drug. The PI at each site was responsible for evaluating all AEs for causality using the following guide:

- Unrelated: clinical event with an incompatible time relationship to study drug administration, and that could be explained by underlying disease or other drugs or chemicals.
- Unlikely: clinical event for which the time relationship to study drug administration makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals.
- Possible: clinical event with reasonable time relationship to study drug administration, but that could also be explained by concurrent disease or other drugs or chemicals.
- Probable: clinical event with a reasonable time relationship to study drug administration, and is unlikely to be attributed to concurrent disease or other drugs or chemicals.
- Definite: clinical event with plausible time relationship to study drug administration, and that cannot be explained by concurrent disease or other drugs or chemicals.

The AEs were reported and documented on the relevant pages of the case report form (CRF), in accordance with the procedures outlined below. The PI at each site was responsible for evaluating all AEs for expectedness in addition to causality and severity.

Drug-related AEs were defined as those with a possible, probable or definite relationship to the study drug. The site PI was asked to assess causality and record this as a 'yes' or 'no' in the CRF.

Adverse event reporting period

The AE reporting period for this trial began on enrolment into the trial and ended 30 days following the last administration of the study drug. All AEs assessed by the PI as possibly or probably related to the study drug and all SAEs that occurred during this time were followed until they were resolved or were clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Adverse event reporting

Because the HARP-2 trial was recruiting from a population that was already in a life-threatening situation, it was expected that many of the participants would experience AEs. Events that were expected in this population (i.e. events that were in keeping with the patient's underlying medical condition) were not required to be reported as AEs.

An adverse reaction (AR) is an AE that is related to the administration of the study drug. Any AEs that were related to the study drug were reported on the AE form within the CRF.

The following are ARs that were expected and reported on the AE form within the CRF:

- CK level of > 10 times the upper limit of normal
- ALT/AST level of > 8 times the upper limit of normal.

An unexpected adverse reaction (UAR) is an AE that is related to the administration of the study drug and that is unexpected, in that it has not been previously reported in the current summary of product characteristics (SPC). Clinicians were instructed to report all UARs.

Serious adverse event reporting

A SAE was defined as an AE that fulfilled one or more of the criteria for severity:

- results in death
- is immediately life-threatening
- requires hospitalisation or prolongs existing hospitalisation
- results in persistent or significant disability or incapacity
- results in congenital abnormality or birth defect
- requires medical intervention to prevent one of the above, or is otherwise considered medically significant.

Because the HARP-2 trial was recruiting from a population that was already in a life-threatening situation, it was expected that many of the participants would experience SAEs. Events that were expected in this population (i.e. events that were in keeping with the patient's underlying medical condition) and that were collected as outcomes of the trial, including death and organ failure, were not reported as SAEs.

The SAEs were evaluated by the PI for causality (i.e. their relationship to study drug) and expectedness. All other SAEs were reported using the SAE form in the patient's CRF and were reported to the CTU within 24 hours of the clinician becoming aware of the event. The CTU was responsible for reporting SAEs to the sponsors, ethics committees, MHRA and IMB within the required timelines as per the regulatory requirements.

A serious adverse reaction (SAR) is a SAE that is related to the administration of the study drug. The following SAR was expected and clinicians were advised that it must be reported on the SAE form within the CRF:

- need for renal replacement therapy in patients with CK levels of > 10 times the upper limit of normal.

The SUSARs are SAEs that are considered to be caused by the study drug and are unexpected (i.e. their nature or severity is not consistent with the SPC). All SUSARs were the subject of expedited reporting to meet regulatory requirements.

All AEs and SAEs were classified using common terminology criteria for adverse events (CTCAE) version 4 (v4.03, 14 June 2010) apart from those AEs/SAEs that were protocol related. According to CTCAE v4.0, elevated ALT, AST and CK fall under the broad category of investigations. However, these AEs were expected ARs in this trial and, as such, they have been presented separately.

When CK levels were elevated and required renal replacement therapy, this SAR fell under the musculoskeletal category and was also reported separately.

Data collection

Hospital data

The Acute Physiology and Chronic Health Evaluation (APACHE) II scores were used as part of the description of the trial population. For centres that participated in the Intensive Care National Audit and Research Centre (ICNARC) Case Mix Programme (CMP), the APACHE II scores were obtained from ICNARC; therefore, these centres supplied only the CMP number for HARP-2 trial participants. Centres that did not participate in the CMP collected all of the data to allow calculation of the APACHE II score.

At enrolment, the patients' demographic characteristics, ventilatory and physiological variables and admission APACHE II scores were recorded. The cause of ARDS was identified by the treating clinician. For each day in the ICU, ventilatory and physiological variables as well as data on organ support based on the UK's critical care minimum data set[40] were recorded. Vital status at 28 days was collected but cause of death was not recorded.

Data were collected and recorded on a two-part carbonised CRF by the site research team from the time the patient was considered for entry into the trial through to their discharge from hospital. In the event that a patient was transferred to another hospital, the site research team liaised with the receiving hospital to ensure complete data collection. On completion of the data collection period, the PI signed off the CRF; the top copy of each CRF was returned to the CTU and the bottom copy was retained in the CRF booklet at the recruiting site. Submitted data were reviewed for completeness on receipt at the CTU and entered onto a secure, backed-up custom database. Entries on the CRF that were ambiguous, unintelligible or incomplete were queried with the hospital research staff who completed the CRF.

Discharge and follow-up questionnaires

To provide an economic evaluation, a HRQoL questionnaire was measured using the EuroQol-5 Dimensions, three-level version (EQ-5D-3L) questionnaire administered at hospital discharge by site staff. The CTU followed up surviving patients with a further EQ-5D questionnaire at 3, 6 and 12 months post randomisation. Resource utilisation data were also collected at 6 and 12 months.

To minimise the risk of causing distress by contacting relatives of patients who had since died, the CTU used a NHS central register and/or contacted the patient's general practitioner (GP) to ascertain the patient's survival status prior to any contact being made.

If questionnaires were not returned, a maximum of two telephone contacts were made to the patient to check that the questionnaire had been received and that the patient was happy to complete it. In the event that the patient stated non-receipt, a second copy of the questionnaire was sent out. If the second questionnaire was not returned, the patient was contacted again by telephone to follow up. To increase the percentage of questionnaire returns an amendment was submitted to the ethics committee to obtain permission to change our procedures to send out a £5 (€5 for sites in Ireland) gift voucher with the first questionnaire as a thank you gesture for patients taking part in the study.

Methods for assays

The MMP-8, IL-6, Ang 2 and RAGE were measured using Duoset enzyme-linked immunosorbent assay kits from R&D Systems Europe (Oxford, UK). According to the manufacturer's instructions, samples were run neat or in reagent diluent (phosphate-buffered saline/1% bovine serum albumin) to obtain values within the detection range of the standard curve. When neat values were less than the lowest standard, then they were assigned the value of the lowest standard. The range of detection for the analyses was as follows.

- MMP-8: 31–4000 pg/ml
- IL-6: 9–600 pg/ml
- Ang2: 94–6000 pg/ml
- RAGE: 62.5–4000 pg/ml.

The CRP was measured by immunoturbidimetric assay performed by Randox Laboratories (Crumlin, Northern Ireland). The range of detection was 0.3–402 mg/l.

Plasma 25-hydroxyvitamin D was measured by liquid chromatography mass spectrometry by colleagues in the laboratory of Barbara Obermayer-Pietsch, Heidelberg, Germany. Values at or below the lower limit of detection were assigned a value of 6.99 ng/ml.

Statistical methods

Analyses were conducted on all outcome data obtained from all participants as randomised and regardless of protocol adherence (i.e. intention-to-treat analysis). All statistical tests were at the two-sided *p*-value of 0.05 unless adjustment for multiple testing was needed. As VFDs and oscillator frequency-free days (OFFDs) had a bimodal distribution, the groups were initially analysed by *t*-test with difference in means and 95% CIs presented. A secondary analysis of these outcome measures involving a bootstrapped *t*-test was also conducted to support the findings of the *t*-tests as detailed in version 3 of the statistical analysis plan. This differed from the main analysis for VFDs detailed in the protocol but was approved by the Trial Steering Committee and independent Data Monitoring and Ethics Committee (DMEC). The comparison of other continuous outcomes was by analysis of variance, including covariates when appropriate. Statistical diagnostic methods were used to check for violations of the assumption, and transformations were performed when required. A statistical interaction test was used to assess differences in treatment effects between the subgroups. For binary outcome measures, risk ratios and associated 95% CIs were calculated. Time-to-event data were presented using Kaplan–Meier plots. In all time-to-event analyses, patients who did not experience the event in question (e.g. death) were censored on the date last seen or 60 days. Time-to-event data were tested using a log-rank chi-squared test. Hazard ratios (HRs) were calculated to test the difference between the treatment groups using the Cox proportional hazards model. All HRs were presented with a two-sided 95% CI. Median follow-up time was calculated.

Subgroup analyses used a statistical test for interaction and were reported using 99% CI.

Four subgroup analyses were prespecified by:

1. age in quartiles
2. vasopressor requirement (defined as any inotropic requirement except dopamine of < 6 µg per kg per minute) as presence or absence
3. sepsis versus non-sepsis aetiology
4. CRP level at baseline in quartiles.

Every effort was made to minimise missing baseline and outcome data in this trial and imputation was not used.

Exploratory analysis on organ dysfunction was carried out using the Mann–Whitney *U*-test.

Exploratory analysis on biomarkers was carried out using student *t*-tests and Fisher's exact test, presented graphically by day, when applicable, and split by baseline quartiles.

Sample size calculation

Sample size assumptions were based on previously published data. Assuming a mean number of VFDs of 12.7 days [standard deviation (SD) 10.6 days],[41] we estimated that a sample of 524 patients would need to be enrolled in order for the study to have 80% power, at a two-tailed significance level of 0.05, to detect a mean between-group difference of 2.6 VFDs. On the basis of data from the Pulmonary Artery Catheters in Management of Patients in Intensive Care (PAC-Man) trial,[42] a dropout rate of 3% was estimated and, therefore, a total of 540 patients (270 in each group) was required.

When the primary outcome measure of VFDs was available for 270 patients, a sample size review was undertaken by the DMEC independent statistician. The purpose of this was to check that the within-groups variance was not substantially underestimated, which would mean that the sample size had been underestimated.

No other data were analysed. The group allocation of the patients was not revealed and this review did not compare the two groups to examine treatment effects. In keeping with recommendations on interim sample size review,[43] the review would not lead to a reduction of the sample size. The review led to a recommendation that the sample size remained unchanged.

Ethics and regulatory approvals

Ethics approval was given for the study by ORECNI REC B (UK sites: 10/NIR02/36) in September 2010 and by CREC (ROI sites: 8/10) in July 2010. Local approval and permission from the research and development (R&D) department of each participating trust was received prior to sites commencing on the study. This was not applicable to Republic of Ireland-based sites.

The MHRA gave approval for the study in August 2010 (UK sites: 32485/0020/001-0001) [and IMB (now Health Products Regulatory Authority)] gave approval in October 2010 (CT900/495/1).

During the trial, the following amendments were submitted to ethics and regulatory authorities.

Amendment one (main changes)

Protocol v1.0_24.06.10 was submitted to ORECNI in the original application for ethics approval. ORECNI requested some changes that necessitated amending the protocol to v2.0_01.09.10. The major changes included:

- amending the exclusion criteria to exclude non-English-speaking patients or those who did not adequately understand verbal or written information unless an interpreter was available
- amending the exclusion criteria to include the wording 'currently' and 'sustained' in relation to the use of listed concomitant medications. Amiodarone was added to the list of concomitant medications
- giving clarification that the 80-mg dose was given as two 40-mg tablets
- adding SOFA score to the schedule of assessments in day 14 and day 28.

Amendment two (main changes)

Protocol v2.0_01.09.10 was amended to v3.0_16.05.11. ORECNI and MHRA approved the following changes.

- Change of address of the chief investigator.
- Non-pulmonary organ failure-free days added to secondary outcomes.
- An additional blood sample was added at day 21 to measure CK and liver function.
- The exclusion criteria were amended to allow for patients receiving erythromycin as a prokinetic to be included in the study.
- Change of address of study drug supplier.
- Other changes: additional sites added.

Amendment three (main changes)

Protocol v3.0_16.05.11 was amended to v4.0_18.07.11 and was approved by ORECNI and MHRA to include the following changes.

- The exclusion criteria were amended to remove clarithromycin and erythromycin.
- Clarification was given that domiciliary ventilation used for sleep-disordered breathing would not be included as mechanical ventilation.
- Scheduling for research samples submission was changed to allow that research samples due on bank holidays or weekends could be collected up to 2 days after the due date (with the exception of day 1).

Amendment four
There was no change to the protocol. Additional sites were added.

Amendment five (main changes)
Protocol v4.0_18.07.11 was amended to v5.0_13.01.12. This amendment was approved by ORECNI and MHRA to include the following change.

- The exclusion criteria were amended to change the upper limit of normal for ALT and AST from more than five times the upper limit of normal to more than eight times the upper limit of normal.

Amendment six (main changes)
Protocol v5.0_13.01.12 was amended to v6.0_09.01.13. This amendment was approved by ORECNI and MHRA to include the following changes.

- The protocol was amended to allow NICTU to use a NHS central register and/or contact the patient's GP to ascertain the patient survival status prior to any contact being made.
- The PIS and consent form were amended to inform patients and patient representatives of this change.
- A GP letter was created to advise the patient's GP of future NICTU contact in relation to patient survival status.

Amendment seven (main changes)
Additional sites added and change of PI at three sites.

Minor amendments included:

- the inclusion of a £5 or €5 thank-you voucher
- change of CTU (NICTU) address from Education and Research Centre to Elliott Dynes Building.

Chapter 3 Results

Overview of recruitment

Patients were recruited between 21 December 2010 and 13 March 2014. During the recruiting period to the HARP-2 trial a total of 40 sites participated in the study: five in Ireland, four in Northern Ireland, four in Scotland and 27 in England. One site opened in 2010, 25 in 2011, nine in 2012, four in 2013 and one in 2014 (*Table 1*).

By July 2011 recruitment was behind target, due to:

- a longer than anticipated trial start-up, relating in part to delays with local R&D permissions
- patients being excluded because they were on clarithromycin or erythromycin.

To address this situation, a substantial amendment was submitted and authorised, allowing the removal of clarithromycin and erythromycin from the exclusion criteria. This had a significant effect on recruitment as 10% of patients screened were excluded owing to patients receiving these drugs. In addition, a further amendment was submitted and authorised to change the upper limit of normal for AST and ALT from five times the upper limit of normal to eight times the upper limit of normal.

A full-time trial co-ordinator commenced in post in December 2011. This allowed the trial manager to commit more time to progressing the opening of new sites. An expression of interest was sent out and attracted > 20 applications. Twelve of these sites were invited to apply on a competitive basis, which resulted in seven new sites joining the study.

In addition, a contract variation was submitted to extend the study for a further 1 year. This extension was approved and allowed a longer period for recruitment (*Figure 1*). As a result of these amendments recruitment to the study increased steadily and the recruitment target was achieved. There was no evidence of recruitment fatigue over the course of the trial.

An ongoing review of sites not meeting the recruitment target was carried out and as a result of this a total of five sites were closed to recruitment over the recruitment period of the study: one in Ireland (closed October 2012), one in Scotland (closed July 2012) and three in England (July 2012, September 2013 and December 2013) (see *Table 1*).

An extension of 1 year was granted in April 2012, at which point the timeline for target recruitment was extended by 1 year. Recruitment was completed in March 2014 when the target of 540 was met.

Participants

Out of the 5926 patients who were assessed for eligibility, 540 (9%) underwent randomisation. Four patients who did not fulfil the eligibility criteria were randomised in each group and are included in the analysis. Five patients allocated to simvastatin and three patients in the placebo group did not receive study drug. One patient in the simvastatin group was lost to follow-up. No data on the primary outcome were available for one patient in the simvastatin group and two patients in the placebo group (*Figure 2*).[37]

Data collection and procedures

To ensure that accurate, complete and reliable data were collected, the CTU provided training to site staff in the format of investigator meetings and/or site initiation visits. The CTU provided the PI and research staff with training on good clinical practice, the study protocol, completion of the CRF and trial procedures including standard operating procedures.

TABLE 1 The HARP-2 trial sites' recruitment

	Time period								
	2011		2012		2013		January to March 2014		
Sites	Screened	Recruited	Screened	Recruited	Screened	Recruited	Screened	Recruited	Total recruited
Addenbrookes	26	3	60	9	157	10	45	5	27
Aintree					23	2	13	1	3
Altnagelvin	85	2	74	5	74	3	13	1	11
Antrim	25	3	28	4	45	11	17	3	21
Arrowe Park, Wirral					21	2	15	3	5
Berkshire (Royal)	50	3	44	3	69	2	18	0	8
Birmingham Heartlands	105	7	98	20	46	9	9	4	40
Bristol	39	8	43	7	48	5	11	0	20
Coventry	30	2	45	8	78	3	34	1	14
Derby (Royal)	35	2	3	0	0	0	0	0	2
Dumfries and Galloway	24	4	29	6	28	5	5	2	17
Edinburgh (Royal Infirmary)	123	6	173	6	129	8	27	1	21
Freemans	61	4	85	5	50	3	18	2	14
Frenchay					27	2	10	2	4
Glasgow Victoria	21	3	31	5	19	3	3	1	12
Glasgow Western	47	2	27	0	0	0	0	0	2
Good Hope	12	0	34	5	27	5	3	0	10
Guy's and St Thomas'	58	5	36	8	48	6	5	1	20
Harefield	7	0	16	1	0	0	0	0	1
Hull			33	2	58	2	16	2	6
King's College London	33	6	116	27	110	9	16	5	47

Sites	Time period								
	2011		2012		2013		January to March 2014		
	Screened	Recruited	Screened	Recruited	Screened	Recruited	Screened	Recruited	Total recruited
Leeds General Infirmatory and St James'			1	1	46	3	9	0	4
Norfolk and Norwich			12	2	21	5	3	1	8
Papworth	45	3	26	2	28	1	11	0	6
Poole			29	5	26	9	4	2	16
Queen Elizabeth Birmingham			26	6	233	19	27	1	26
Royal Free Hospital							30	1	1
Royal Hospitals Belfast	156	23	99	17	127	18	23	2	60
Royal Liverpool			86	5	191	10	32	4	19
Royal Preston			35	1	42	1	5	0	2
Royal Sussex					68	4	8	0	4
St George's Hospital			70	2	35	0	0	0	2
Ulster Hospital	56	9	103	6	80	3	15	3	21
Whiston	148	4	143	12	178	4	41	3	23
Worcester (Royal)	20	2	27	4	18	3	2	0	9
Beaumont Hospital			54	6	33	1	6	0	7
Cork	7	0	33	5	23	4	3	0	9
Galway	12	5	99	6	77	4	17	0	15
Mater			44	0	0	0	0	0	0
St Vincent's Hospital			18	3	19	0	5	0	3
Total	1225	106	1880	204	2302	179	519	51	540

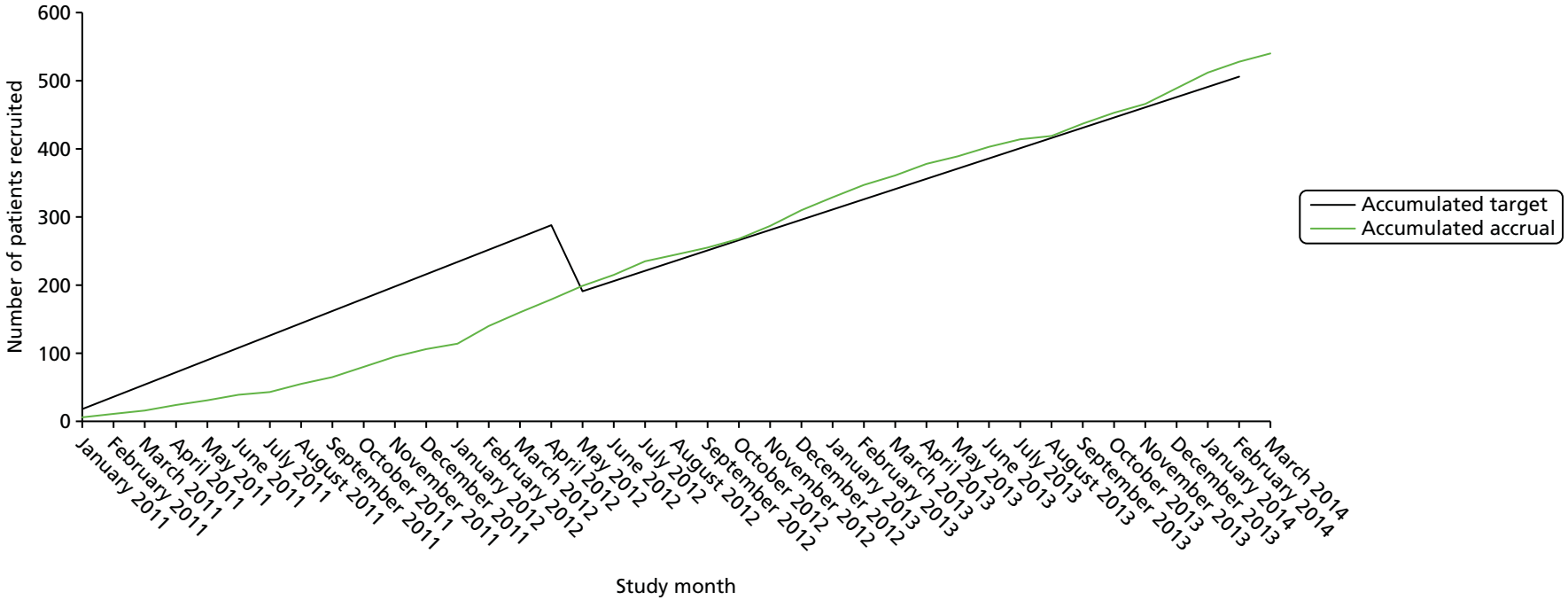

FIGURE 1 The HARP-2 trial monthly accrual.

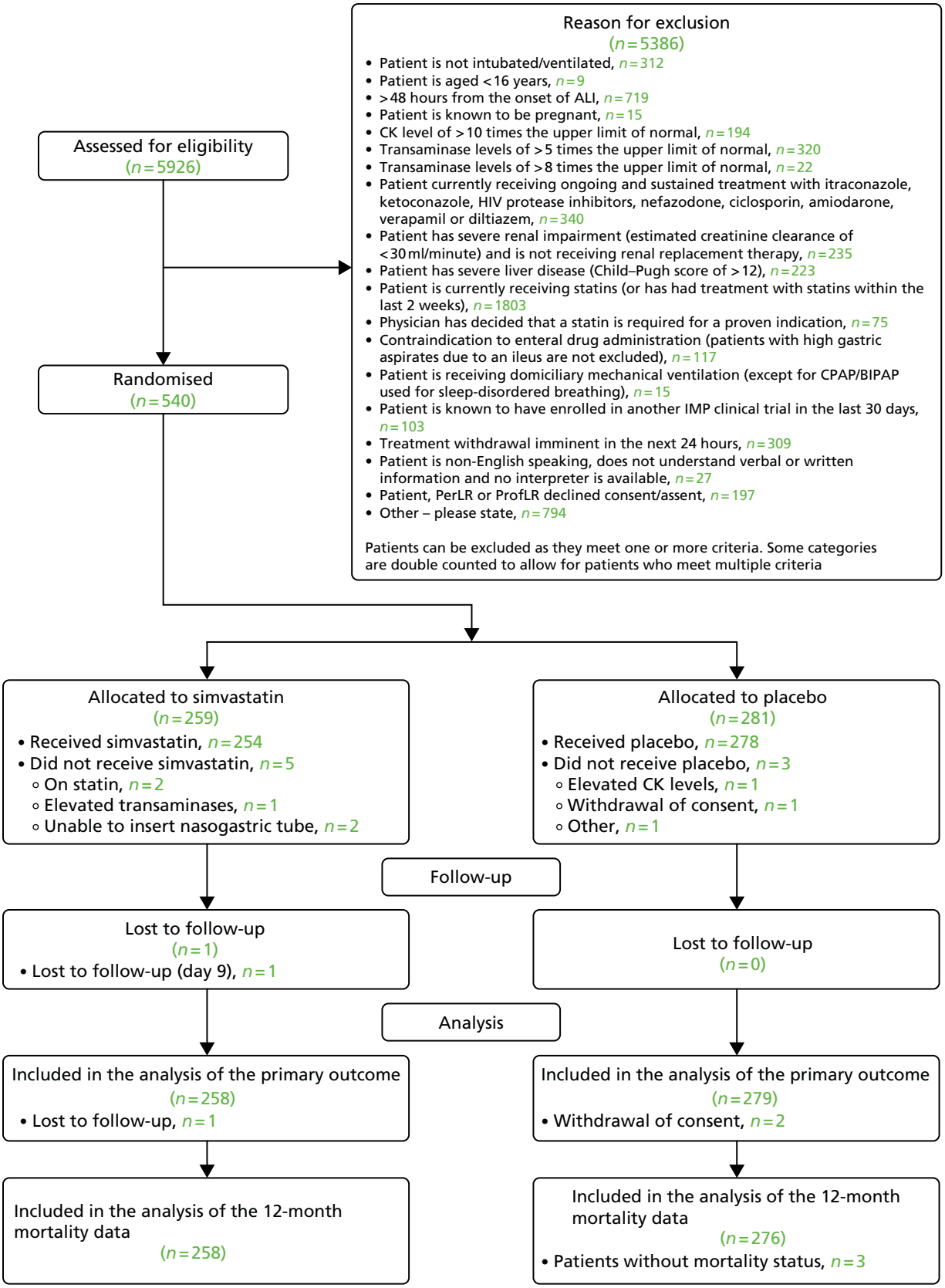

FIGURE 2 Flow chart of 12-month mortality BIPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; IMP, investigational medicinal product. From *The New England Journal of Medicine*, McAuley DF, Laffey MD, O'Kane CM, Perkins GD, Mullan B, Trinder J, *et al.* Simvastatin in the acute respiratory distress syndrome, vol. 371, pp. 1695–703.[37] Copyright © 2014 Massachusetts Medical Society. Reprinted with permission.

Baseline characteristics

The baseline characteristics of the patients at randomisation were similar in the two study groups. The main causes of ARDS were pneumonia and sepsis. On day 3, the tidal volume in the simvastatin group did not differ significantly from that in the placebo group; the mean difference was 0.05 ml per kg of predicted body weight (95% CI −0.61 to 0.71 ml per kg; $p = 0.89$) (*Table 2*).[37]

TABLE 2 Baseline characteristics at trial entry

Characteristic	Treatment group	
	Simvastatin ($n = 259$)	Placebo ($n = 280$)
Age (years), mean (SD)	53.2 (16.1)	54.4 (16.7)
Gender, *n* (%)		
Male	137 (52.9)	170 (60.7)
Female	122 (47.1)	110 (39.3)
Sepsis, *n* (%)	189 (73.0)	218 (77.9)
Non-sepsis, *n* (%)	70 (27.0)	62 (22.1)
Vasopressor requirement, *n* (%)		
Yes	169 (65.2)	187 (66.8)
No	90 (34.8)	93 (33.2)
Plateau pressure (cm H_2O), mean (SD)	23.55 (6.07)	23.64 (6.03)
APACHE II score, mean (SD)	19.4 (6.9)	18.3 (6.2)
$PaO_2 : FiO_2$ ratio, mean (SD)	16.4 (7.3)	17.6 (7.4)
Tidal volume per ideal body weight (ml/kg), mean (SD)	8.1 (2.8)	8.1 (2.6)
Aetiology of ARDS		
Direct, *n* (%)		
Smoke/toxin inhalation	1 (0.4)	2 (0.7)
Gastric content aspiration	21 (8.1)	29 (10.4)
Near drowning	0 (0)	0 (0)
Thoracic trauma	22 (8.5)	10 (3.6)
Pneumonia	161 (62.2)	154 (55.0)
Other	15 (5.8)	19 (6.8)
Indirect, *n* (%)		
Sepsis	106 (40.9)	118 (42.1)
Cardiopulmonary bypass	1 (0.4)	0 (0)
Pancreatitis	5 (1.9)	17 (6.1)
Non-thoracic trauma	4 (1.5)	8 (2.9)
Other	14 (5.4)	1 9 (6.8)
SOFA score, mean (SD)	8.60 (3.2)	8.97 (2.9)
OI, mean (SD)	112.8 (87.3)	112.0 (89.0)
Lowest mean arterial pressure (mmHg), mean (SD)	65.4 (9.3)	64.9 (8.4)

Mean (SD) is presented for continuous data and the number (%) is presented for categorical data for the baseline information.

Treatment with study drug

Patients received the study drug for a mean of 10.2 days (SD 7.1 days) in the simvastatin group and 11.0 days (SD 7.9 days) in the placebo group ($p = 0.23$). The most common reasons for discontinuation of the study drug were discharge from critical care, death and an AE that was considered to be related to the study drug. A total of five patients assigned to the simvastatin group and three assigned to the placebo group received treatment with non-trial statins.

Table 3 presents the mean (SD) for continuous data and the number (%) for categorical data for treatment after trial entry, reasons for termination of study drug and protocol violations.[37]

TABLE 3 Treatment after trial entry

	Treatment group	
Study drug administration	**Simvastatin ($n = 259$)**	**Placebo ($n = 280$)**
Study drug given	254	278
Number of days on treatment, mean (SD)	10.2 (7.1)	11 (7.9)
Reason for termination of study drug,* n *(%)		
28 days after randomisation	20 (7.7)	28 (10.0)
Discharge from critical care	141 (54.4)	147 (52.3)
Liver transaminases levels of > 5/8 times upper limit	20 (7.7)	16 (5.7)
CK levels of > 10 times upper limit	21 (8.1)	14 (5.0)
Request for discontinuation of trial drug by patient or legal representative	2 (0.8)	3 (1.1)
Discontinuation of active treatment	9 (3.5)	8 (2.8)
Development of a condition requiring immediate treatment with statin	2 (0.8)	3 (1.1)
Decision by a physician on safety ground	3 (1.2)	4 (1.4)
Death	31 (12.0)	46 (16.4)
Other	10 (3.9)	12 (4.3)
Non-trial statins	5 (–)	3 (–)
Days of non-trial statins, mean (SD)	6 (8)	3 (2)
***Protocol violations,* n**		
Post-randomisation withdrawal		
Refused use of data already collected	0	1
Refused data collection from NHS records	0	1
Withdrew from follow-up	1	4
Ineligible patient	4	4
Did not receive allocated treatment	5	3
Received treatment of other group	0	0
Study drug administered in error	27	24
Study drug omitted in error	21	31

–, only *n* presented.

From *The New England Journal of Medicine*, McAuley DF, Laffey MD, O'Kane CM, Perkins GD, Mullan B, Trinder J, *et al.* Simvastatin in the acute respiratory distress syndrome, vol. 371, pp. 1695–703.[37] Copyright © 2014 Massachusetts Medical Society. Reprinted with permission.

As a marker of compliance and absorption, simvastatin concentrations were measured in plasma samples used for biomarker analyses. Simvastatin or simvastatin acid were detectable in plasma in 216 out of 226 (96%) samples from simvastatin-treated patients at day 3. Of the 10 participants in whom simvastatin was not detected at day 3, five had detectable concentrations of simvastatin at day 7. One subject had documented withholding of medication at day 3 and 7.

Because this was not a true pharmacokinetic measurement (i.e. the samples not taken in relation to timing of drug administration), the levels were highly variable and potentially less than the limit of detection of the assay in subjects assigned to simvastatin in the four remaining subjects in whom it was not detectable at days 3 or 7.

Outcomes

Primary outcome

The number of VFDs did not differ significantly between the two study groups (*Table 4*) [12.6 days (SD 9.9 days) with simvastatin and 11.5 days (SD 10.4 days) with placebo; mean difference 1.1 days, 95% CI −0.6 to 2.8 days; $p = 0.21$].[37] There was also no significant between-group difference in the number of VFDs after adjustment for the baseline $PaO_2 : FiO_2$ ratio (mean difference 1.4 days, 95% CI −0.3 to 3.2 days; $p = 0.10$).

TABLE 4 Short-term outcomes

Outcome	Treatment group			
	Simvastatin	Placebo	Difference (95% CI); results from bootstrapped *t*-test	*p*-value; results from bootstrapped *t*-test
Primary outcome; VFDs to 28 days post randomisation[a]				
n	258	279		
Mean (SD)	12.6 (9.9)	11.5 (10.4)	1.1 (–0.6 to 2.8); 1.1 (–0.7 to 2.8)	0.21; 0.22[a]
Non-pulmonary OFFDs in first 28 days ($N = 539$)				
n	257	279		
Mean (SD)	19.4 (11.1)	17.8 (11.7)	1.6 (–0.4 to 3.5); 1.6 (–0.3 to 3.5)	0.11; 0.10[a]
Change in OI from baseline ($N = 404$)				
Day 3 ($n = 329$)				
n	167	162		
Mean (SD)	–25.3 (59.7)	–8.5 (75.1)	–16.8 (–31.5 to –2.1)	0.02
Day 7 ($n = 204$)				
n	93	111		
Mean (SD)	–33.0 (83.9)	–30.1 (78.5)	–2.9 (–25.4 to 19.5)	0.80
Day 14 ($n = 100$)				
n	43	57		
Mean (SD)	–37.5 (111.3)	–24.6 (61.8)	–13.0 (–47.7 to 21.7)	0.46
Day 28 ($n = 19$)				
n	4	15		
Mean (SD)	20.7 (125.4)	–54.0 (43.6)	74.7 (–3.5 to 153.0)	0.06

TABLE 4 Short-term outcomes (*continued*)

Outcome	Treatment group			
	Simvastatin	Placebo	Difference (95% CI); results from bootstrapped *t*-test	*p*-value; results from bootstrapped *t*-test
Change in SOFA from baseline ($N = 472$)				
Day 3 ($n = 430$)				
n	205	225		
Mean (SD)	–0.9 (2.2)	–0.8 (2.3)	–0.1 (–0.5 to 0.3)	0.67
Day 7 ($n = 307$)				
n	152	155		
Mean (SD)	–2.5 (3.0)	–2.5 (2.7)	–0.1 (–0.7 to 0.6)	0.86
Day 14 ($n = 151$)				
n	70	81		
Mean (SD)	–3.4 (3.3)	–2.4 (3.2)	–1.1 (–2.1 to –0.01)	0.047
Day 28 ($n = 38$)				
n	15	23		
Mean (SD)	–4.1 (3.9)	–2.7 (4.3)	–1.5 (–4.3 to 1.3)	0.29
All-cause mortality 28 days post randomisation[b]	57/259 (22.0)	75/280 (26.8)	0.8 (0.6 to 1.1)	0.23
Death before discharge from critical care[b]	56/259 (21.6)	70/280 (25.0)	0.9 (0.6 to 1.2)	0.36
Death before discharge from hospital[b]	67/259 (25.9)	90/280 (32.1)	0.8 (0.6 to 1.1)	0.13

Mean (SD) presented for treatment groups.
a Results from bootstrapped *t*-test.
b *n* (%) for treatment groups and risk ratio and 95% CI presented.
From *The New England Journal of Medicine*, McAuley DF, Laffey MD, O'Kane CM, Perkins GD, Mullan B, Trinder J, *et al.* Simvastatin in the acute respiratory distress syndrome, vol. 371, pp. 1695–703.[37] Copyright © 2014 Massachusetts Medical Society. Reprinted with permission.

Short-term secondary outcomes

The change from baseline to day 28 in the OI (*Figure 3* and see *Table 4*) did not differ significantly between the two groups, nor did the SOFA score (*Figure 4* and see *Table 4*).[37] There were no significant differences in the number of days free of non-pulmonary organ failure or in mortality at 28 days (see *Table 4*).[37] Mortality at ICU discharge or hospital discharge (see *Table 4*) was also not significantly different between the two groups.[37] Among survivors, the mean duration of the ICU stay was 13.9 days (SD 14.4 days) in the simvastatin group and 14.4 days (SD 13.3 days) in the placebo group (mean difference –0.5 days, 95% CI –3.2 to 2.2 days; $p = 0.71$). The mean duration of the hospital stay was 37.7 days (SD 64.5 days) and 35.4 days (SD 31.1 days) for the simvastatin group and the placebo group, respectively (mean difference 2.3 days, 95% CI –8.0 to 12.6 days; $p = 0.66$). From randomisation to day 28, there were no significant differences between the two groups in the probability of breathing without assistance or the probability of survival (*Figure 5*).[37]

Bootstrapped *t*-test for non-pulmonary OFFDs was not statistically significant (mean difference 1.6 days, 95% CI –0.3 to 3.5 days; $p = 0.10$). To adjust for the multiple testing for the change in OI and total SOFA score, a *p*-value of 0.0125 is considered to be statistically significant.

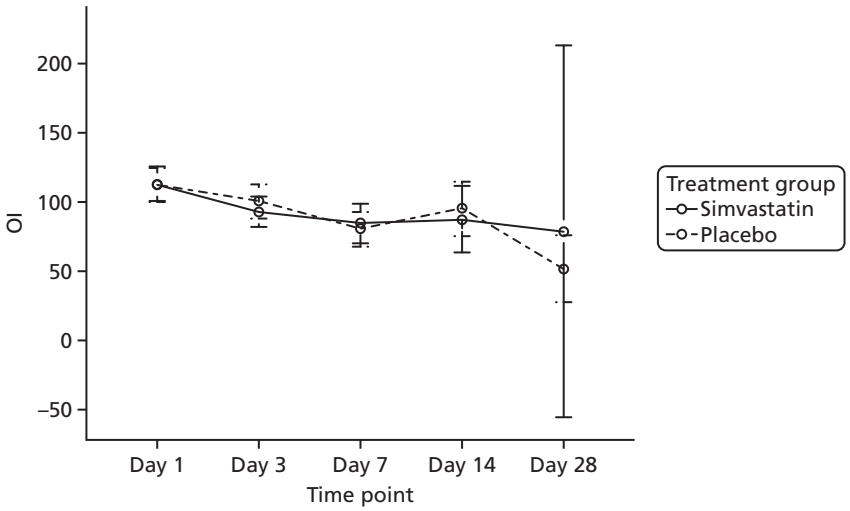

FIGURE 3 The OI and 95% CI at days 1, 3, 7, 14 and 28.

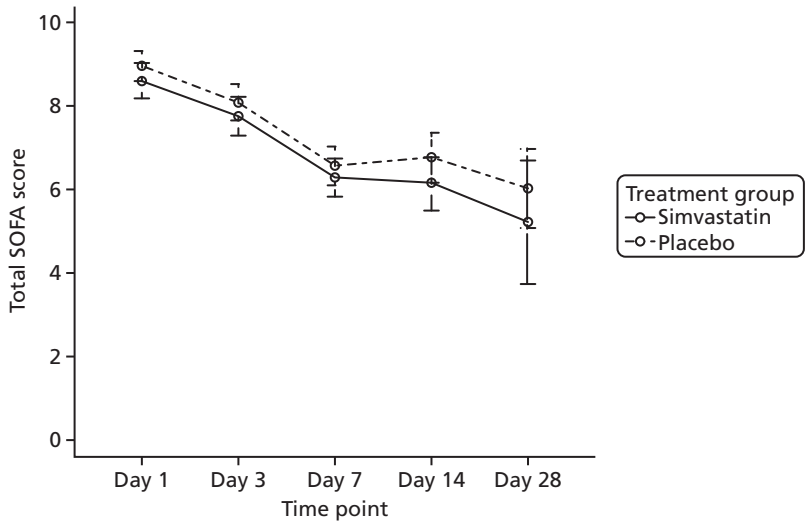

FIGURE 4 Mean SOFA score and 95% CI at days 1, 3, 7, 14 and 28.

Exploratory analyses

The SOFA is a secondary outcome for this study (*Table 5*).[37] Further exploratory analysis was carried out for non-pulmonary dysfunction. There was no significant between-group difference in the proportion of patients with non-pulmonary organ dysfunction, as measured by a SOFA score of < 2 for each organ.

Exploratory biomarker analysis

Neutrophil activation

Neutrophil activation, as measured by plasma MMP-8 concentrations, was compared at baseline and day 3 between the statin and placebo treatment groups. There was no baseline difference between the two groups (difference 4352.00 pg/ml, 95% CI –3410.15 to 12,114.15 pg/ml). Simvastatin did not reduce MMP-8 at day 3 (*Figure 6*) (difference –1138.12 pg/ml, 95% CI –6895.97 to 4619.74 pg/ml).

Patients were stratified into quartiles according to degree of neutrophil activation at baseline to investigate whether or not those with greater baseline inflammation had a greater response to simvastatin. We found no evidence that high neutrophil activation at baseline predicted a response to simvastatin in terms of VFDs or 28-day mortality (*Tables 6* and *7*).

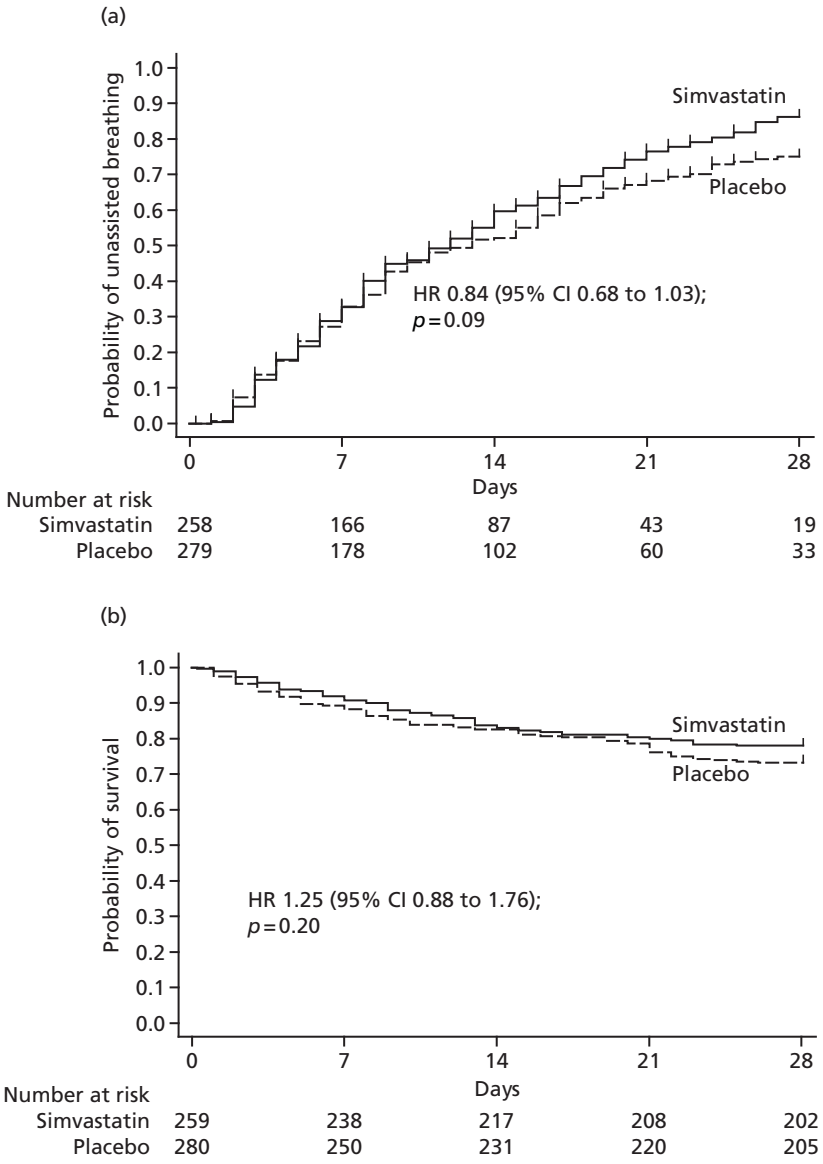

FIGURE 5 Kaplan–Meier plot for probabilities of survival at 28 days and breathing without assistance, from the day of randomisation (day 0) to day 28, according to whether patients received simvastatin or placebo. (a) Unassisted breathing; and (b) survival. From *The New England Journal of Medicine*, McAuley DF, Laffey MD, O'Kane CM, Perkins GD, Mullan B, Trinder J, *et al.* Simvastatin in the acute respiratory distress syndrome, vol. 371, pp. 1695–703.[37] Copyright © 2014 Massachusetts Medical Society. Reprinted with permission.

We found no evidence that higher neutrophil activation at baseline predicted a reduction in neutrophil activation at day 3 with simvastatin treatment (*Table 8*).

Systemic inflammation and acute phase response

Previously in the HARP study[26] simvastatin was shown to reduce systemic inflammation in patients with ARDS. We assessed the effect of simvastatin on systemic inflammation and acute phase response, as measured by IL-6 and CRP levels.

Baseline CRP level was the same in the statin and placebo-treated groups (difference –4.8 mg/l, 95% CI –24.0 to 14.5 mg/l). Although CRP levels fell over time, there was no difference between placebo and simvastatin-treated cohorts at day 3 (difference –5.5 mg/l, 95% CI –23.0 to 12.0 mg/l) (*Figure 7* shows mean and SD CRP for simvastatin- and placebo-treated groups).

TABLE 5 Exploratory organ dysfunction analysis: proportion of patients with a SOFA score of < 2 by organ, according to study group[a]

	Day, *n*/*N*														
	1			3			7			14			28		
Variable	Simvastatin	Placebo	*p*-value	Simvastatin	Placebo	*p*-value	Simvastatin	Placebo	*p*-value	Simvastatin	Placebo	*p*-value	Simvastatin	Placebo	*p*-value
Renal	220/247	235/271	0.4	220/249	224/264	0.3	184/202	180/205	0.3	96/106	101/118	0.3	32/34	35/37	1.0
Hepatic	206/240	223/269	0.4	215/247	216/261	0.2	183/198	177/202	0.1	93/102	102/113	1.0	31/32	33/36	0.6
Cardiovascular	81/259	80/280	0.5	123/253	131/267	0.9	160/203	169/209	0.6	92/110	98/123	0.5	34/36	36/39	1.0
Haematological	188/247	210/270	0.7	183/249	200/261	0.5	172/201	175/204	1.0	97/106	109/118	0.8	30/34	33/37	1.0
Neurological	166/241	182/263	1.0	159/237	174/256	0.8	127/188	132/202	0.7	65/103	67/115	0.5	17/32	17/37	0.6

a Scores on the SOFA scale range from 0 to 24, with higher scores indicating more severe disease. Scores of < 2 indicate no significant organ dysfunction.

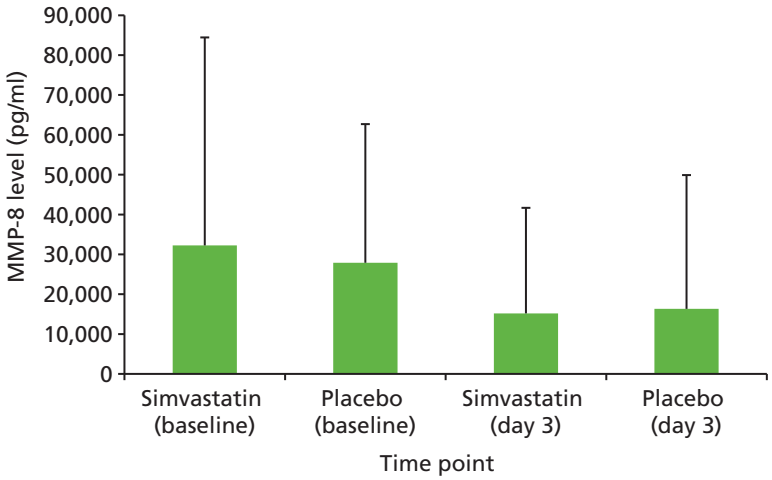

FIGURE 6 Mean (SD) plasma MMP-8 (pg/ml) levels in simvastatin- and placebo-treated groups at baseline and day 3.

TABLE 6 Ventilator-free days to day 28 post randomisation in simvastatin- and placebo-treated groups according to baseline MMP-8 quartile

	Treatment group, mean (SD)		
VFDs to 28 days post randomisation	Simvastatin	Placebo	Difference (99% CI)
MMP-8 (pg/ml)			
≤ 5191 ($n = 124$)	15.54 (9.54)	13.12 (10.96)	2.41 (–2.40 to 7.23)
5191–13,792 ($n = 123$)	11.07 (10.15)	12.32 (10.81)	–1.25 (–6.22 to 3.72)
13,792–34,631 ($n = 124$)	11.87 (9.81)	10.06 (9.88)	1.81 (–2.87 to 6.49)
> 34,631 ($n = 124$)	11.35 (9.44)	10.44 (10.18)	0.91 (–3.71 to 5.53)

TABLE 7 Mortality at 28 days post randomisation in simvastatin- and placebo-treated groups according to baseline MMP-8 quartile

	Treatment group, *n* (%)				
	Simvastatin		Placebo		
Mortality at 28 days post randomisation	Dead	Alive	Dead	Alive	*p*-value
MMP-8 (pg/ml)					
≤ 5191	10 (14.71)	58 (85.29)	13 (22.81)	44 (77.19)	0.26
5191–13,792	16 (28.07)	41 (71.93)	16 (23.88)	51 (76.12)	0.68
13,792–34,631	9 (16.98)	44 (83.02)	21 (29.58)	50 (70.42)	0.14
> 34,631	14 (23.33)	46 (76.67)	20 (31.25)	44 (68.75)	0.42

TABLE 8 Neutrophil activation: MMP-8 level at day 3 in simvastatin- and placebo-treated groups according to baseline MMP-8 quartile

MMP-8 (pg/ml) level at baseline quartiles	Treatment group					
	Simvastatin		Placebo			
	Mean (SD)	*n*	Mean (SD)	*n*	Difference (95% CI)	*p*-value
≤ 5191	7121.02 (9869.97)	59	7402.07 (14,578.1)	46	–281.05 (–5022.03 to 4459.92)	0.907
> 5191 and ≤ 13,792	12,316.53 (27,271.85)	52	18,072.60 (48,578.34)	61	–5756.07 (–20,797.17 to 9285.03)	0.450
> 13,792 and ≤ 34,631	17,620.51 (32,966.06)	44	17,527.61 (24,428.20)	55	92.90 (–11,359.92 to 11,545.72)	0.987
> 34,631	24,806.60 (30,740.25)	49	21,661.31 (33,229.70)	48	3145.29 (–9754.41 to 16,044.99)	0.630

Data are mean (SD) and treatment groups are compared by independent *t*-test.

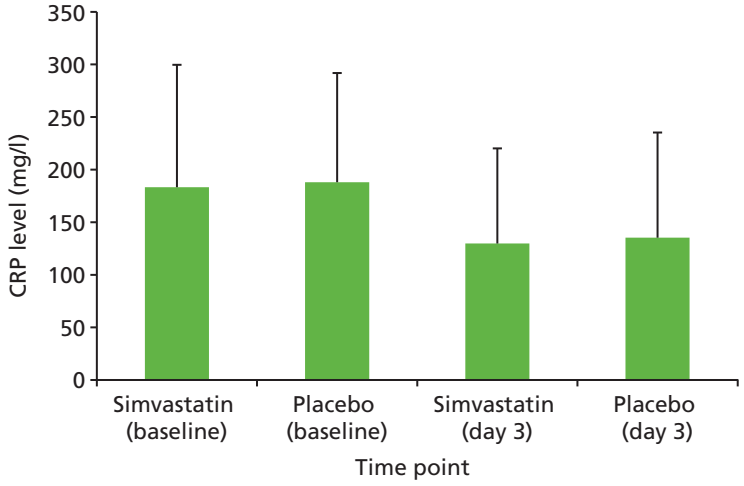

FIGURE 7 Systemic inflammation: mean (SD) plasma CRP levels in simvastatin- and placebo-treated groups at baseline and day 3.

We tested the hypothesis that simvastatin would have a greater effect in those with higher baseline acute phase response, reflecting increased inflammation. Patients were stratified into quartiles according to baseline CRP level. There was no evidence that higher baseline CRP level predicted a greater response to simvastatin in terms of either reducing VFDs or 28-day mortality (*Tables 9* and *10*).

There was no evidence that a greater degree of baseline inflammation predicted a greater response to simvastatin as measured by systemic CRP at day 3 (*Table 11*).

Plasma IL-6, a marker of systemic inflammation, was measured in patients at baseline (difference –45.03 pg/ml, 95% CI –342.61 to 252.54 pg/ml) and day 3 (difference 14.10 pg/ml, 95% CI –33.22 to 61.42 pg/ml). There was no difference in baseline level nor day 3 IL-6 level between the two groups (*Figure 8*).

Patients were stratified into quartiles according to baseline IL-6 level to test the hypothesis that higher inflammation at recruitment, as measured by plasma IL-6 level, predicted a greater response to simvastatin. Higher baseline IL-6 level did not predict a greater response to simvastatin in terms of VFDs (*Table 12*) or 28-day mortality (*Table 13*).

TABLE 9 Ventilator-free days to day 28 post randomisation in simvastatin- and placebo-treated groups according to baseline CRP-level quartile

VFDs to 28 days post randomisation	Treatment group		Difference (99% CI)
	Simvastatin	Placebo	
CRP (mg/l) level at baseline, mean (SD)			
≤ 100 (*n* = 125)	11.8 (10.4)	9.0 (10.7)	2.8 (–2.1 to 7.8)
100–175 (*n* = 122)	13.5 (10.5)	13.2 (10.2)	0.3 (–4.6 to 5.2)
175–250 (*n* = 134)	12.9 (9.8)	11.2 (10.9)	1.7 (–3.1 to 6.5)
> 250 (*n* = 126)	12.7 (9.0)	12.0 (9.6)	0.7 (–3.7 to 5.0)

TABLE 10 Mortality at 28 days post randomisation in simvastatin- and placebo-treated groups according to baseline CRP-level quartile

Mortality at 28 days post randomisation	Treatment group, *n* (%)				
	Simvastatin		Placebo		
	Dead	Alive	Dead	Alive	*p*-value
CRP (mg/l) level					
≤ 100 (*N* = 126)	18 (26.09)	51 (73.91)	17 (29.82)	40 (70.18)	0.692
100–175 (*N* = 124)	15 (25.42)	44 (74.58)	14 (21.54)	51 (78.46)	0.674
175–250 (*N* = 134)	10 (17.54)	47 (82.46)	27 (35.06)	50 (64.94)	0.032
> 250 (*N* = 126)	9 (14.52)	53 (85.48)	13 (20.31)	51 (79.69)	0.484

Table 12 presents the *n* (%) alive/dead by treatment group and corresponding *p*-value taken from Fisher's exact test.

TABLE 11 Day 3 CRP (mg/l) level in simvastatin- and placebo-treated groups according to baseline CRP-level quartile

CRP (mg/l) level at baseline quartiles	Treatment group					
	Simvastatin		Placebo			
	Mean (SD)	*n*	Mean (SD)	*n*	Difference (95% CI)	*p*-value
≤ 100	65.38 (49.94)	48	79.70 (64.21)	63	–14.33 (–36.53 to 7.88)	0.204
> 100 and ≤ 175	112.08 (79.90)	60	105.82 (62.05)	53	6.26 (–20.67 to 33.19)	0.646
> 175 and ≤ 250	160.75 (95.04)	65	149.06 (85.00)	53	11.69 (–21.55 to 44.93)	0.487
> 250	186.99 (117.35)	58	184.83 (98.29)	56	2.16 (–38.08 to 42.40)	0.916

Data are mean (SD) and treatment groups are compared by independent *t*-test.

We did not find that higher baseline levels of IL-6 predicted a greater reduction in systemic inflammation as measured by IL-6 by day 3 (*Table 14*).

As a sterol-based hormone (steroid), vitamin D rises during the acute inflammatory response. We investigated whether or not simvastatin affected circulating plasma 25-hydroxyvitamin D during the course of ARDS. There was no baseline difference between the two groups (difference –0.14, 95% CI –1.47 to 1.19) and no evidence that simvastatin altered plasma vitamin D during the course of ALI (*Figure 9*).

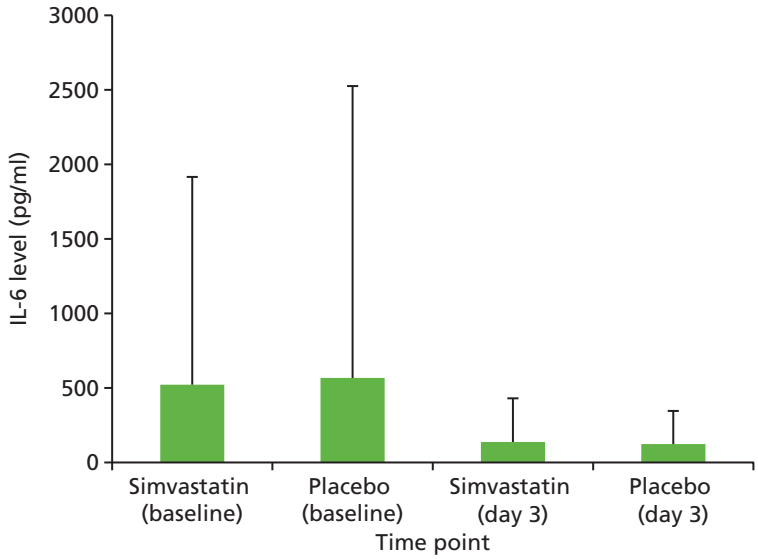

FIGURE 8 Systemic inflammation: mean (SD) plasma IL-6 (pg/ml) level in simvastatin- and placebo-treated groups at baseline and day 3.

TABLE 12 Ventilator-free days to 28 days post randomisation in simvastatin- and placebo-treated groups according to baseline IL-6-level quartile

	Treatment group, mean (SD)		
VFDs to 28 days post randomisation	Simvastatin	Placebo	Difference (99% CI)
IL-6 (pg/ml) level			
≤ 52.89 ($n = 127$)	15.59 (10.11)	11.86 (10.42)	3.73 (–1.04 to 8.49)
52.89–135.15 ($n = 126$)	13.49 (9.20)	13.02 (10.72)	0.48 (–4.17 to 5.12)
135.15–349.15 ($n = 128$)	11.51 (9.88)	11.92 (10.75)	–0.41 (–5.29 to 4.47)
> 349.15 ($n = 127$)	9.66 (9.66)	8.95 (9.64)	0.71 (–3.77 to 5.19)

TABLE 13 Mortality at 28 days post randomisation in simvastatin- and placebo-treated groups according to baseline IL-6-level quartile

	Treatment group, *n* (%)				
	Simvastatin		Placebo		
Mortality at 28 days post randomisation	Dead	Alive	Dead	Alive	*p*-value
IL-6 (pg/ml) level					
≤ 53	9 (14.29)	54 (85.71)	11 (16.92)	54 (83.08)	0.81
53–135	13 (19.12)	55 (80.88)	9 (15.25)	50 (84.75)	0.64
135–349	12 (22.64)	41 (77.36)	26 (34.67)	49 (65.33)	0.17
> 349	18 (29.03)	44 (70.97)	26 (40.00)	39 (60.00)	0.26

n (%) alive/dead by treatment group and corresponding *p*-value taken from Fisher's exact test.

TABLE 14 Day 3 IL-6 levels in simvastatin- and placebo-treated groups according to baseline IL-6-level quartile

	Treatment group					
	Simvastatin		Placebo			
IL-6 (pg/ml)-level baseline quartiles	Mean (SD)	*n*	Mean (SD)	*n*	Difference (95% CI)	*p*-value
≤ 53	59.59 (160.41)	56	47.90 (60.73)	60	11.68 (–32.37 to 55.73)	0.60
> 53 and ≤ 135	67.96 (74.0)	65	57.93 (65.35)	53	10.04 (–15.72 to 35.79)	0.442
> 135 and ≤ 349	115.87 (137.02)	47	132.15 (214.82)	68	–16.28 (–86.59 to 54.03)	0.647
> 349	312.57 (504.44)	57	227.94 (291.99)	56	84.63 (–69.37 to 238.63)	0.279

Data are mean (SD) and treatment groups are compared by independent *t*-test.

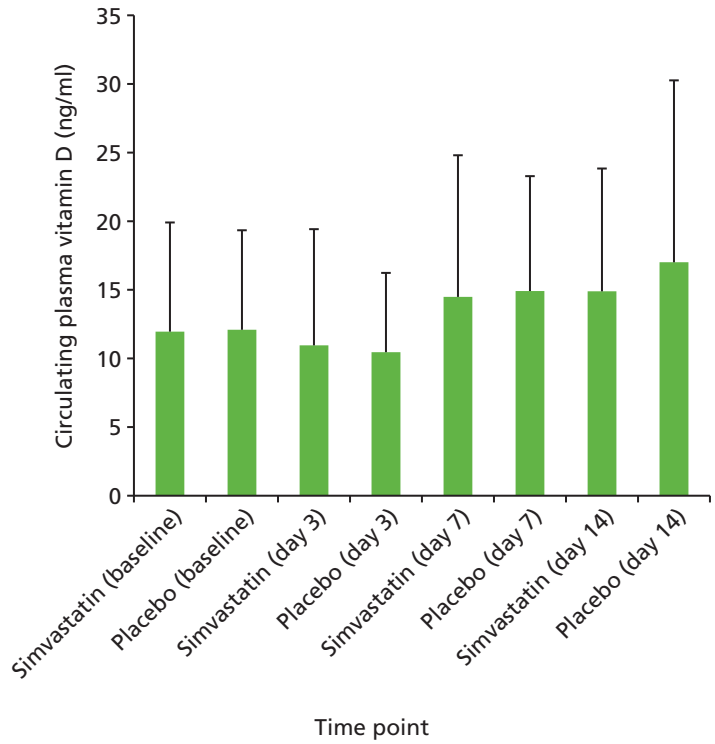

FIGURE 9 Acute phase response: mean (SD) circulating plasma vitamin D level in simvastatin- and placebo-treated groups at baseline and days 3, 7 and 14.

Patients were stratified into quartiles according to baseline vitamin D. There was no evidence that those with higher vitamin D at baseline who received simvastatin had a greater improvement in VFDs or reduction in mortality than those receiving placebo (*Tables 15* and *16*).

We did not find that higher baseline levels of vitamin D predicted a greater reduction in acute phase response as measured by vitamin D on day 3 (*Table 17*).

Endothelial injury

Endothelial injury as measured by plasma Ang2 concentrations was compared at baseline and day 3 between the statin and placebo treatment groups. There was no difference in baseline (difference 1153.44 pg/ml, 95% CI –4644.16 to 6951.03 pg/ml) or day 3 (difference 541.09 pg/ml, 95% CI –498.46 to 1580.65 pg/ml) between the two groups (*Figure 10*).

TABLE 15 Ventilator-free days to day 28 post randomisation in simvastatin- and placebo-treated groups according to baseline vitamin D quartile

	Treatment group, mean (SD)		
Primary outcome	Simvastatin	Placebo	Difference (99% CI)
25-hydroxyvitamin D level (ng/ml)			
< 7[a] (*n* = 198)	12.63 (9.95)	11.65 (10.64)	0.98 (–2.85 to 4.81)
≥ 7 and ≤ 9 (*n* = 55)	14.63 (8.84)	7.60 (9.85)	7.03 (0.30 to 13.77)
> 9 and ≤ 14 (*n* = 125)	11.92 (9.84)	11.85 (9.95)	0.07 (–4.57 to 4.70)
> 14 (*n* = 126)	12.32 (10.49)	11.89 (10.81)	0.42 (–4.55 to 5.40)

a < 7 converted to 6.99 for purposes of analysis.

TABLE 16 Mortality at 28 days post randomisation in simvastatin- and placebo-treated groups according to baseline vitamin D quartile

	Treatment group, *n* (%)				
	Simvastatin		Placebo		
Secondary outcome	Dead	Alive	Dead	Alive	*p*-value
25-hydroxyvitamin D level (ng/ml)					
< 7 (*N* = 198)	19 (20.43)	74 (79.57)	32 (30.19)	74 (69.81)	0.143
≥ 7 and ≤ 9 (*N* = 55)	2 (6.67)	28 (93.33)	9 (36.00)	16 (64.00)	0.015
> 9 and ≤ 14 (*N* = 126)	16 (25.40)	47 (74.60)	16 (25.40)	47 (74.60)	1.000
> 14 (*N* = 126)	16 (26.67)	44(73.33)	15 (22.73)	51 (77.27)	0.681

n (%) alive/dead by treatment group and corresponding *p*-value taken from Fisher's exact test.

TABLE 17 Day 3 vitamin D in simvastatin- and placebo-treated groups according to baseline vitamin D quartile

	Treatment group					
	Simvastatin		Placebo			
25-hydroxyvitamin D level at baseline quartiles	Mean (SD)	*n*	Mean (SD)	*n*	Difference (95% CI)	*p*-value
25-hydroxyvitamin D level (ng/ml)						
≤ 6.99[a]	8.03 (2.25)	83	7.57 (1.57)	96	0.46 (–0.11 to 1.02)	0.115
> 6.99 and ≤ 8.9	8.83 (4.03)	29	8.72 (3.67)	23	0.10 (–2.07 to 2.28)	0.924
> 8.9 and ≤ 14.325	9.36 (4.29)	56	9.80 (4.19)	54	–0.44 (–2.04 to 1.17)	0.591
> 14.325	17.40 (13.36)	56	16.89 (7.47)	55	0.51 (–3.57 to 4.59)	0.805

a < 7 converted to 6.99 for purposes of analysis.
Data are mean (SD) and treatment groups are compared by independent *t*-test.

Patients were stratified into quartiles according to degree of endothelial injury at baseline to investigate whether or not those with greater baseline endothelial injury had a greater response to simvastatin. We found no evidence that higher endothelial injury at baseline predicted a response to simvastatin in terms of VFDs or 28-day mortality (*Tables 18* and *19*).

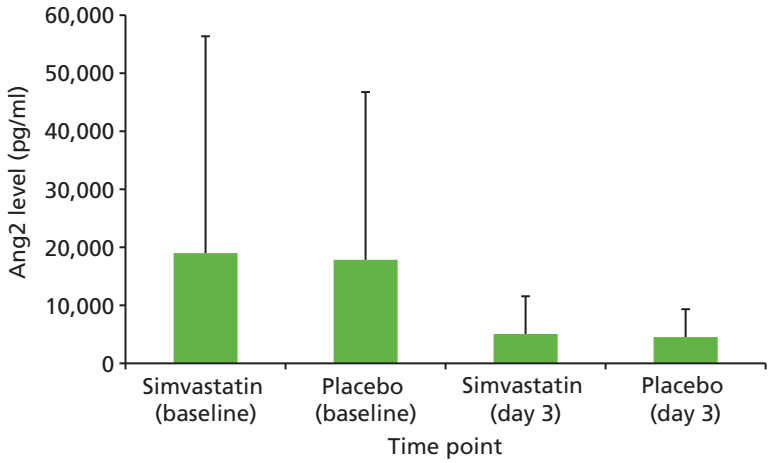

FIGURE 10 Endothelial injury: mean (SD) plasma Ang2 (pg/ml) level in simvastatin- and placebo-treated groups at baseline and day 3.

TABLE 18 Ventilator-free days to day 28 post randomisation in simvastatin- and placebo-treated groups according to baseline Ang2 quartile

	Treatment group, mean (SD)		
VFDs to 28 days post randomisation	Simvastatin	Placebo	Difference (99% CI)
Ang2 (pg/ml) level			
≤ 4369 ($n = 127$)	13.82 (9.78)	11.88 (11.00)	1.94 (–2.89 to 6.76)
4369–10,308 ($n = 126$)	13.65 (9.81)	11.55 (10.16)	2.10 (–2.56 to 6.77)
10,308–23,761 ($n = 127$)	12.91 (9.90)	12.69 (9.95)	0.22 (–4.42 to 4.86)
> 23,761 ($n = 127$)	10.30 (9.92)	9.06 (10.55)	1.24 (–3.51 to 5.99)

TABLE 19 Mortality at 28 days post randomisation in simvastatin- and placebo-treated groups according to baseline Ang2 quartile

	Treatment group, *n* (%)				
	Simvastatin		Placebo		
Mortality at 28 days post randomisation	Dead	Alive	Dead	Alive	*p*-value
Ang2 (pg/ml) level					
≤ 4369	12 (17.65)	56 (82.35)	16 (26.67)	44 (73.33)	0.29
4369–10,308	13 (21.67)	47 (78.33)	17 (25.37)	50 (74.63)	0.68
10,308–23,76	10 (17.86)	46 (82.14)	17 (23.94)	54 (76.06)	0.51
> 23,761	17 (26.98)	46 (73.02)	22 (34.38)	42 (65.63)	0.44

n (%) alive/dead by treatment group and corresponding *p*-value taken from Fisher's exact test.

We did not demonstrate that higher Ang2 at baseline predicted a response to simvastatin in terms of showing reduced endothelial injury at day 3 (*Table 20*).

Alveolar epithelial injury

Type I alveolar epithelial cell injury as measured by plasma RAGE concentrations was compared at baseline (difference 31.83 pg/ml, 95% CI –102.96 to 166.62 pg/ml) and day 3 (difference 103.43 pg/ml, 95% CI –71.54 to 278.40 pg/ml) between the statin and placebo treatment groups (*Figure 11*). Simvastatin had no effect on plasma RAGE.

TABLE 20 Day 3 Ang2 in simvastatin- and placebo-treated groups according to baseline Ang2 quartile

	Treatment group					
	Simvastatin		Placebo			
Ang2 (pg/ml)-level baseline quartiles	Mean (SD)	*n*	Mean (SD)	*n*	Difference (95% CI)	*p*-value
≤ 4369	2890.95 (2330.86)	63	3122.72 (2835.92)	52	–231.78 (–1186.16 to 722.61)	0.631
> 4369 and ≤ 10,308	4302.81 (6989.11)	54	3769.17 (3067.72)	56	533.64 (–1493.92 to 2561.19)	0.603
> 10,308 and ≤ 23,761	5393.56 (5071.44)	51	4675.61 (4621.78)	68	717.95 (–1049.96 to 2485.87)	0.423
> 23,761	7831.79 (8899.61)	58	6364.04 (6913.79)	59	1467.75 (–1447.80 to 4383.30)	0.321

Data are mean (SD) and treatment groups are compared by independent *t*-test.

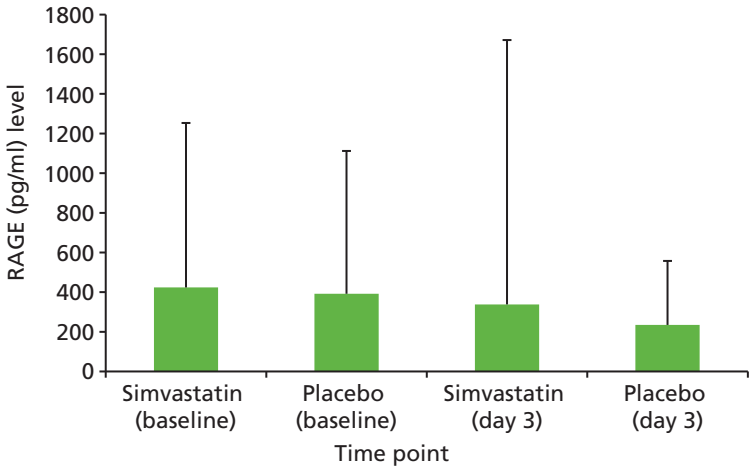

FIGURE 11 Epithelial injury: mean (SD) plasma RAGE (pg/ml) level in simvastatin- and placebo-treated groups at baseline and day 3.

Patients were stratified into quartiles according to degree of epithelial injury at baseline to investigate whether or not those with evidence of greater epithelial injury at recruitment had a differential response to simvastatin. We found no evidence that worse epithelial injury at baseline predicted a response to simvastatin in terms of VFDs (*Table 21*) or 28-day mortality (*Table 22*).

In addition, we did not find that higher epithelial injury at baseline predicted a greater response to simvastatin in terms of reducing plasma RAGE at day 3 (*Table 23*).

TABLE 21 Ventilator-free days to day 28 post randomisation in simvastatin- and placebo-treated groups according to baseline RAGE quartile

	Treatment group, mean (SD)		
VFDs to 28 days post randomisation	Simvastatin	Placebo	Difference (99% CI)
RAGE (pg/ml) level			
≤ 63 (*n* = 167)	12.70 (9.36)	12.69 (10.38)	0.01 (–3.98 to 4.00)
> 63 and ≤ 124 (*n* = 87)	12.82 (10.69)	9.83 (10.21)	2.99 (–2.93 to 8.91)
> 124 and ≤ 369 (*n* = 128)	14.29 (10.04)	11.68 (10.54)	2.61 (–2.16 to 7.37)
> 369 (*n* = 127)	10.92 (9.88)	10.68 (10.62)	0.24 (–4.52 to 5.01)

TABLE 22 Mortality at 28 days post randomisation in simvastatin- and placebo-treated groups according to baseline RAGE quartile

Mortality at 28 days post randomisation	Treatment group, *n* (%)				
	Simvastatin		Placebo		
	Dead	Alive	Dead	Alive	*p*-value
RAGE (pg/ml) level					
≤ 63 (*N* = 168)	11 (13.10)	73 (86.90)	25 (29.76)	59 (70.24)	0.014[a]
> 63 and ≤ 124 (*N* = 88)	9 (23.08)	30 (76.92)	10 (20.41)	39 (79.59)	0.799
> 124 and ≤ 369 (*N* = 128)	13 (20.97)	49 (79.03)	18 (27.27)	48 (72.73)	0.419
> 369 (*N* = 127)	19 (30.65)	43 (69.35)	19 (29.23)	46 (70.77)	1.000

a As there are four comparisons being made, a statistically significant value would be < 0.0125.
n (%) alive/dead by treatment group and corresponding *p*-value taken from Fisher's exact test.

TABLE 23 Day 3 RAGE in simvastatin- and placebo-treated groups according to baseline RAGE quartile

RAGE (pg/ml)-level baseline quartiles	Treatment group					
	Simvastatin		Placebo			
	Mean (SD)	*n*	Mean (SD)	*n*	Difference (95% CI)	*p*-value
≤ 63	147.30 (235.06)	79	160.77 (213.85)	76	–13.47 (–84.87 to 57.92)	0.710
> 63 and ≤ 124	79.12 (36.70)	38	208.72 (442.53)	44	–129.59 (–273.00 to 13.81)	0.076
> 124 and ≤ 369	167.41 (167.68)	54	273.32 (375.67)	58	–105.92 (–216.25 to 4.42)	0.060
> 369	948.16 (2587.01)	56	305.42 (257.06)	59	642.74 (–27.83 to 1313.30)	0.060

Data are mean (SD) and treatment groups are compared by independent *t*-test.

In summary, the biomarker exploratory analyses did not indicate that simvastatin treatment had any effect on neutrophilic inflammation, systemic inflammation or the acute phase response, nor on alveolar epithelial or endothelial injury in this cohort of patients. We were not able to identify a subgroup of patients with ALI as determined by levels of baseline systemic inflammation or epithelial or endothelial injury who had any beneficial effect from simvastatin.

Subgroup analysis

Subgroup analyses did not suggest that the effects of simvastatin were modified by any of the variables investigated. There was no significant interaction between treatment and age ($p = 0.62$), vasopressor requirement ($p = 0.17$), presence or absence of sepsis ($p = 0.50$) (*Table 24*)[37] or baseline CRP level ($p = 0.77$) (see *Table 9*).

Long-term outcomes

Mortality at 12 months post randomisation was a long-term clinical outcome for the trial and was not statistically significantly different between the two groups ($p = 0.20$; *Table 25* and *Figure 12*[44]).

TABLE 24 Subgroup analysis by age, vasopressor requirement and sepsis

Primary outcome: VFDs to 28 days post randomisation	Treatment group, mean (SD)		Difference (99% CI)
	Simvastatin	Placebo	
Age (years)			
≤ 42.3 ($n = 133$)	15.8 (9.2)	13.4 (9.8)	2.4 (–1.9 to 6.7)
42.3–54.3 ($n = 134$)	13.5 (9.7)	14.3 (10.3)	–0.8 (–5.3 to 3.7)
54.3–66.3 ($n = 134$)	11.5 (9.9)	10.3 (10.3)	1.2 (–3.4 to 5.7)
> 66.3 ($n = 134$)	9.3 (10.1)	8.1 (10.2)	1.1 (–3.5 to 5.7)
Vasopressor requirement			
Absent ($n = 182$)	14.7 (10.1)	11.9 (10.4)	2.8 (–1.2 to 6.8)
Present ($n = 353$)	11.5 (9.7)	11.2 (10.4)	0.3 (–2.5 to 3.1)
Sepsis/non-sepsis			
Sepsis ($n = 404$)	12.2 (10.1)	10.8 (10.3)	1.4 (–1.2 to 4.0)
Non-sepsis ($n = 131$)	13.7 (9.6)	13.6 (10.7)	0.05 (–4.6 to 4.7)

From *The New England Journal of Medicine*, McAuley DF, Laffey MD, O'Kane CM, Perkins GD, Mullan B, Trinder J, *et al.* Simvastatin in the acute respiratory distress syndrome, vol. 371, pp. 1695–703.[37] Copyright © 2014 Massachusetts Medical Society. Reprinted with permission.

TABLE 25 Mortality at 12 months post randomisation

Outcome	Treatment group		Risk ratio (95% CI)	*p*-value (Fisher's exact test)
	Simvastatin	Placebo		
Mortality 12 months post randomisation, *n*/*N* (%)	82/258 (31.8)	103/276 (37.3)	0.9 (0.7 to 1.1)	0.20

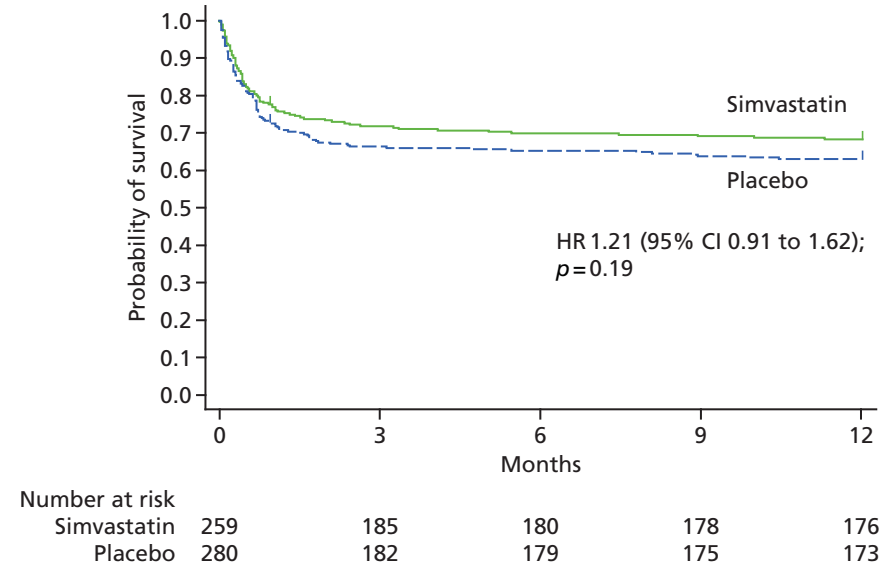

FIGURE 12 Kaplan–Meier plot for 12-month survival. Amended from Agus *et al.*[44] This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

Adverse events

Safety outcomes

A total of 121 patients experienced AEs and a total of 170 AEs were reported in the study. The SAEs were reported in 25 patients (11 patients in the simvastatin group and 14 patients in the placebo group). In total, 28 SAEs were reported (12 in the simvastatin group and the 16 in the placebo group), with one patient in the simvastatin group having two SAEs and two patients in the placebo group each having two SAEs. In the simvastatin group one SAE was assessed to be related to study drug and this was not assessed to be an unexpected SAE. In the placebo group three SAEs were assessed to be related to study drug and, of these, two were thought to be unexpected SAEs.

There were two SUSARs reported during the HARP-2 study, neither of which was fatal. Both SUSARs were reported to the relevant competent authorities and ethics committee within the applicable 15-day window.

Table 26 summarises AEs, SAEs, SUSARs, ARs and SARs by treatment group.[37] *Table 27* shows that the absolute values of AST and CK were significantly elevated at day 14 in the simvastatin-treated group, and that the elevation in CK persisted to day 21, reflecting the increased incidence of AEs related to CK and elevated transaminases. *Table 27* presents the mean (SD) for highest ALT (units per litre), AST (units per litre) and CK (units per litre) collected over the course of the trial.

TABLE 26 Safety by treatment group

Outcome	Treatment group, *n*		OR (95% CI)	*p*-value
	Simvastatin	Placebo		
AEs, SAEs and SUSARs				
Total number of SAEs; patients	12; 11	16; 14	0.8 (0.3 to 2.0)	0.84
Related to study drug[a]	1	3	0.4 (0.0 to 5.9)	0.61; 0.42[b]
Related to study drug and unexpected[c]	0	2	0.0 (0.0 to 2.6)	0.49; 0.32[b]
Total number of AEs; patients	84; 59	86; 62	1.0 (0.7 to 1.6)	0.92
Related to study drug[a]	45	30	2.2 (1.1 to 4.2)	0.02; 0.01[b]
SAEs				
Cardiac disorders	3	5	0.7 (0.1 to 5.1)	1.00
Gastrointestinal disorders	3	0	[d]	0.07
Hepatobiliary disorders	0	1	0[e]	1.00
Infections and infestations	1	2	0.6 (0.0 to 14.0)	1.00
Injury, poisoning and procedural complications	1	1	1.4 (0.0 to 144.1)	1.00
Musculoskeletal and connective tissue disorders/elevated CK levels	1	1	1.4 (0.0 to 144.1)	1.00
Nervous system disorders	1	2	0.6 (0.0 to 14.0)	1.00
Renal and urinary disorders	1	0	[d]	0.43
Respiratory, thoracic and mediastinal disorders	1	4	0.3 (0.0 to 3.5)	0.36
AEs				
ALT levels of > 8 times the upper limit of normal and/or AST levels of > 8 times the upper limit of normal[f]	34	24	1.8 (0.9 to 3.5)	0.11; 0.06[b]
Blood and lymphatic system disorders	1	1	1.0 (0.0 to 81.3)	1.00

continued

TABLE 26 Safety by treatment group (*continued*)

Outcome	Treatment group, *n*		OR (95% CI)	*p*-value
	Simvastatin	Placebo		
Cardiac disorders	6	11	0.5 (0.2 to 1.6)	0.31
CK levels of > 10 times the upper limit of normal[f]	24	16	1.8 (0.8 to 3.9)	0.15; 0.09[b]
Gastrointestinal disorders	6	4	1.6 (0.4 to 7.9)	0.53
General disorders and administration site conditions	1	3	0.3 (0.0 to 4.3)	0.62
Infections and infestations	2	6	0.3 (0.0 to 1.9)	0.28
Injury, poisoning and procedural complications	1	3	0.3 (0.0 to 4.3)	0.62
Investigations	2	2	1.0 (0.1 to 14.4)	1.00
Nervous system disorders	1	3	0.3 (0.0 to 4.3)	0.62
Renal and urinary disorders	2	2	1.0 (0.1 to 14.4)	1.00
Respiratory, thoracic and mediastinal disorders	4	5	0.8 (0.2 to 3.9)	1.00
Skin and subcutaneous tissue disorders	0	6	0.0 (0.0 to 0.7)	0.03
ARs[a]				
CK levels of > 10 times the upper limit of normal	17	8	2.5 (0.9 to 7.0)	0.05; 0.04[b]
ALT levels of > 8 times the upper limit of normal and/or AST levels of > 8 times the upper limit of normal	26	16	2.0 (0.9 to 4.3)	0.08; 0.05[b]
SARs[a]				
Need for renal replacement therapy in patients with CK elevated > 10-fold	1	1	1.4 (0.0 to 114.1)	1.00

p-values taken from Fisher's exact test.
a The AE or SAE was considered to be due to the study drug if it was considered by the site PI to have a possible, probable or definite relationship to the study drug.
b The results from a one-tailed analysis also presented for safety outcomes.
c AEs were considered to be unexpected if their nature or severity was not consistent with the SPC for simvastatin.
d Could not calculate odds ratio as zero events occurred in the placebo group.
e 95% CI could not be calculated owing to low number of events.
f Frequency of elevated CK and transaminases presented regardless of whether this was assessed to be due to study drug or whether the protocol specified levels of elevated CK and transaminases defining AE were met.
From *The New England Journal of Medicine*, McAuley DF, Laffey MD, O'Kane CM, Perkins GD, Mullan B, Trinder J, *et al.* Simvastatin in the acute respiratory distress syndrome, vol. 371, pp. 1695–703.[37] Copyright © 2014 Massachusetts Medical Society. Reprinted with permission.

Discussion

In this large, multicentre, double-blind, randomised, placebo-controlled clinical trial in patients with ARDS, simvastatin did not improve short- or long-term clinical outcomes. VFDs is a composite measure that includes death. We analysed VFDs overall as well as the composites of duration of ventilation (see *Table 29*) and mortality (see *Table 4* and *Figure 5*[37]) separately, and both were in the same direction. Mortality rates were lower in the simvastatin group, although this was not statistically significant. Owing to the central limit theorem and the large sample size of 540 in the trial, we used a *t*-test (parametric technique) that assumes normality; however, we backed this up with a bootstrapped *t*-test, which is a non-parametric technique and makes no assumptions on the distribution of the data, which in fact was bimodal. Simvastatin was associated with an increase in AEs, but there was no increase in SAEs.

Our biomarker study findings indicated that simvastatin did not modulate pathogenic mechanisms implicated in the development of ALI. ALI is characterised by neutrophilic inflammation and alveolar

TABLE 27 Safety blood descriptive statistics by treatment group

Day	Treatment group, mean (SD)		
	Simvastatin	Placebo	*p*-value[a]
1			
Highest ALT (U/L)	45.5 (47.1)	45.8 (43.2)	
Highest AST (U/L)	59.9 (49.4)	65.3 (63.9)	
Highest CK (U/L)	327.2 (499.3)	298.3 (487.7)	
3			
Highest ALT (U/L)	48.1 (54.9)	65.8 (215.2)	0.47
Highest AST (U/L)	71.3 (103.1)	102.1 (454.1)	0.37
Highest CK (U/L)	414.4 (1001.8)	350.4 (941.5)	0.54
7			
Highest ALT (U/L)	60.0 (63.0)	76.7 (155.7)	0.15
Highest AST (U/L)	65.1 (57.6)	76.9 (153.1)	0.34
Highest CK (U/L)	170.5 (293.4)	183.8 (450.3)	0.70
14			
Highest ALT (U/L)	84.8 (142.1)	74.3 (115.2)	0.59
Highest AST (U/L)	110.7 (218.3)	58.5 (52.5)	0.03
Highest CK (U/L)	409.7 (1350.9)	104.4 (311.9)	0.03
21			
Highest ALT (U/L)	96.2 (110.9)	72.3 (67.9)	0.21
Highest AST (U/L)	64.2 (74.1)	75.5 (126.7)	0.81
Highest CK (U/L)	364.4 (912.2)	77.2 (174.5)	0.03
28			
Highest ALT (U/L)	57.7 (46.9)	105.6 (230.0)	0.30
Highest AST (U/L)	47.0 (54.8)	64.8 (111.5)	0.98
Highest CK (U/L)	219.9 (631.7)	131.3 (317.2)	0.59

U/L, units per litre.
a *p*-values from analysis of covariance adjusting for day 1 (randomisation) values.

epithelial and endothelial cell dysfunction. It is usually accompanied by evidence of systemic inflammation and systemic endothelial dysfunction. Measurement of neutrophil activation by plasma MMP-8 was chosen as this marker is neutrophil-specific, reflects their activation status and is easily and reproducibly measurable in highly inflamed samples. In addition, MMP-8 has been shown to be modulated by simvastatin in our healthy volunteer study of lung injury.[23] CRP is the gold-standard marker of systemic inflammation in clinical care and has been shown to fall in statin-treated ARDS patients in our previous Phase IIa study.[26] IL-6 has been shown in multiple studies to have important baseline predictive value and to correlate better with degree of lung injury and progress of disease in ARDS than many other biomarkers. In addition, we had shown a trend to reduction in IL-6 the statin-treated group in our Phase IIa HARP study.[26]

We have previously identified (McAuley D, O'Kane C. Queen's University Belfast, 2015; unpublished data) a rise in vitamin D concentrations over the course of ARDS, suggesting that it is synthesised as part of a generalised sterol-increase response in stress. We hypothesised that simvastatin would inhibit inflammation and the stress response and that this would be reflected by a reduction in neutrophil activation (MMP-8)

and markers of inflammation/acute phase (CRP, vitamin D and IL-6). RAGE is a type I alveolar epithelial cell injury marker, accounting for the majority of the alveolar epithelial surface. Higher baseline levels of RAGE, indicating greater alveolar injury, are predictive of death in ARDS.

Angiopoietin 2 is a biomarker of endothelial inflammation and has been shown in several studies to be an independent prognostic marker for death in patients with ARDS. Although it is possible that the biomarkers chosen were not the 'best' biomarkers to show the effect of simvastatin, we did choose biomarkers that have been shown to be prognostically and mechanistically important in previous studies in ARDS and that, in the case of IL-6 and CRP, have previously shown a response to simvastatin in an ARDS population (albeit in a small study).[26] The absence of even a trend across this range of markers that reflect the different key pathophysiological mechanisms of ARDS (inflammation, endothelial and epithelial injury and neutrophil activation) correlates with the absence of effect of simvastatin on clinical outcome measures, and supports our conclusion that simvastatin did not modulate these pathophysiological mechanisms. Potential explanations for the absence of effect include potential significant variability in the tissue levels of drug achieved, with levels being inadequate to impair inflammation, or a true absence of these 'off-target' statin effects in patients with disease. It is also possible that by the time ALI has presented clinically, the cascade of inflammation and systemic inflammatory response is already too far advanced to allow statins to have an effect. It is possible that statins are potentially more useful as a pre-treatment strategy to inhibit these mechanisms at the time of onset.

The study was a well-conducted, large, multicentre, allocation-concealed, randomised, double-blind, parallel-group trial. This is the gold standard to determine the potential benefits of a therapeutic intervention and, therefore, it is highly unlikely that deficiencies in the trial design accounted for the lack of difference between the groups.

Statins can modulate mechanisms important in the pathogenesis of ALI.[10] Observational studies support a clinical trial of a statin in ALI.[21] Furthermore, simvastatin reduced LPS-induced pulmonary and systemic inflammation in humans[23] and a proof-of-concept study found that simvastatin improved pulmonary and non-pulmonary organ dysfunction, reduced inflammation and was well tolerated in patients with ALI.[26] Therefore, the rationale for the use of simvastatin was well justified.

One consideration is that the study may have been underpowered. The sample size calculation was based on a between-group difference of 2.6 VFDs. The 95% CI for VFDs was –0.6 to 2.8 days; therefore, it is possible that the study concluded incorrectly that there was no difference between the groups.

A further possibility for the lack of efficacy relates to the statin and dosage used. The choice of 80 mg of simvastatin used was based on our previous data[23,36] that indicated 80 mg of simvastatin improved surrogate clinical outcomes and biological mechanisms believed to be important in the development of ALI. Although the majority of data indicate that the pleotropic effects of statins are likely to be a class effect, we used simvastatin as it was the only statin with proof-of-concept human data. There are also more recent data to indicate that simvastatin may be more effective than atorvastatin,[45] supporting the use of simvastatin in this study. An 80-mg dose of simvastatin is a high dosage; this was selected based not only on our pilot data but also on data from a study in which simvastatin 5 mg/kg and 20 mg/kg were investigated in a murine LPS model of ALI and only the higher dose was effective in attenuating lung injury.[31] Furthermore, observational studies of statin usage in critically ill patients found a greater mortality benefit in patients who were receiving a higher dose of statin.[32] It is possible that adverse effects at the simvastatin dosage used outweighed a beneficial effect. Our data would suggest that this is unlikely given that, although there was a higher incidence of AEs related to simvastatin, the numbers of SAEs were similar in both groups. Furthermore, the higher incidence of AEs did not lead to simvastatin being stopped earlier or more frequently.

Although plasma CRP fell in both groups, there was no difference between the groups. This raises the possibility that the lack of efficacy could mean that the dosage used was not sufficient, or not adequately absorbed to reach therapeutic simvastatin concentrations and we acknowledge that a potential limitation is

that a formal pharmacokinetic/pharmacodynamics study was not undertaken to confirm adequate absorption and drug exposure. However, we demonstrated that simvastatin was present in the patients randomised to simvastatin. We believe that it is likely that an adequate simvastatin concentration was achieved for several reasons. Prior studies in the critically ill indicate that 80 mg of enterally daily administered simvastatin produces systemic drug concentrations that are in the high therapeutic range, and that drug absorption is seen even in patients with high nasogastric aspirates. Furthermore, given that patients in the simvastatin treatment group received the therapy for a mean of 10 days, it would be expected that this would be sufficient to see a treatment effect if one was present. Finally, the increased incidence of expected statin-related AEs would provide support that sufficient simvastatin concentrations were achieved. We believe that the lack of an effect on plasma CRP suggests that statins in ARDS are unable to modulate inflammation sufficiently to translate into a beneficial clinical effect. One potential reason for the absence of an effect may be related to the fact that 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase may already be significantly inhibited as reflected by the low cholesterol levels seen in critically ill patients.

Following on from our previous Phase II study[36] we recruited a heterogenous cohort of patients with ARDS due to any aetiology, which was an attempt to ensure that our findings would be applicable to the overall population of patients with ARDS. The observed mortality in the trial was lower than that described in unselected observational studies. It is recognised that patients who were recruited to clinical trials may represent a selected population owing to the study eligibility criteria, which is further indicated by the fact that only approximately 9% of those meeting the inclusion criteria were subsequently recruited. However, the results of the trial are still generalisable to those patients fulfilling the trial eligibility criteria.

Recent data have suggested that it may be possible to identify subphenotypes within the overall population of patients with ARDS.[46] Although we failed to identify improvements in biological mechanisms implicated in ARDS in the overall cohort, further work could explore if it is possible to identify a population that might be more responsive to simvastatin.

There are frequently reasons, independent of pulmonary status, such as neurological impairment, that may affect the decision to extubate and that may prolong the duration of ventilation. These non-pulmonary factors may not be modifiable regardless of an improvement in pulmonary function. Therefore, it is possible that such factors could have accounted for the absence of any difference in VFDs. However, given the absence of any difference in pulmonary organ dysfunction between the groups, it is less likely that this was a major confounding issue in the finding of no difference in VFDs.

Although we recommended best practice management for ARDS, including lung protective ventilation, we did not measure details of clinical management. At randomisation, the tidal volume was 8.1 ml/kg of predicted body weight and it is possible that this level of tidal volume may have confounded the potential effects of simvastatin. However, this is unlikely given the similar absence of benefit for rosuvastatin in the SAILS study,[12] in which the mean tidal volume was 6.6–6.8 ml/kg of predicted body weight. Our data for tidal volume and plateau pressure are consistent with those seen in other clinical trials in critical care in which ventilation is not strictly protocolised.[47]

Conclusion

In conclusion, our study showed that high dose enteral simvastatin, while safe and with minimal adverse effects, is not effective at improving clinical outcomes in patients with ARDS.

Chapter 4 Economic evaluation

Methods

Aim and perspective

The aim of the economic evaluation was to assess the cost-effectiveness of simvastatin compared with placebo at 12 months. The study was a cost–utility analysis undertaken alongside the main trial. Incremental cost-effectiveness ratios (ICERs) were used to present cost per quality-adjusted life-year (QALY). This ratio represents the difference in mean health service cost of the simvastatin and placebo groups divided by the difference in mean QALYs between groups to establish the cost per QALY gained, in keeping with the recommendations of National Institute for Health and Care Excellence (NICE).[48] The perspective of the analysis was the NHS and Personal Social Services. In addition, data of private and informal care were collected but these were not included in the cost-effectiveness analysis.

Health and social care service use and costs

Data on the health and social care services used by all patients were collected 12 months post randomisation. Data relating to patients' primary hospital admission were collected prospectively via the CRF until primary hospital discharge or death. Data on levels of care and organ support were obtained from the daily data collection section of the CRF. These data (on levels of care and organ support) were only available for a maximum of 28 days or until discharge to a separate HDU or ward. It was assumed that patients were discharged to a rehabilitation ward for respiratory disorders. Other ICU days included the remaining time spent in the ICU after 28 days (if applicable) and any other stay in the ICU during a patient's primary admission, but level of care was not recorded for these ICU days. It was anticipated that some patients would move multiple times between ICU, HDU and the ward during their primary admission, thus, the CRF tracked this movement so that length of stay could be calculated for each. Patients' use of medications other than the study drug was not included in the economic analysis.

Use of health and social care services after hospital discharge was collected retrospectively via questionnaires posted out to surviving patients at 6 and 12 months post randomisation. Mortality status was established prior to posting via contact with the research sites, engagement with the Health and Social Care Information Service (now known as NHS Digital), and contact with GPs. The questionnaire asked patients to report their use of primary and secondary care services, and private and informal care.

Individual-level resource use was combined with unit costs to estimate total costs of health and social care use for each participant in the trial. Unit costs were obtained from publicly available sources and set at 2013–14 prices.

These were *NHS Reference Costs*[49] for hospital resources, the *Unit Costs of Health and Social Care 2014*[50] for general practice services and the *NHS Electronic Drug Tariff*[51] for the cost of simvastatin (*Table 28*).

Health outcomes

The economic analysis used the QALY as the measurement of health outcome. The QALY reflects the impact of an intervention on both the quality and quantity of a patient's life and is recommended by NICE in economic evaluations.[48] QALYs were derived using the EQ-5D-3L.[53] This generic HRQoL instrument, which has been used frequently in the critically ill,[54–56] provides a description of health using five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each with three levels of severity. Patients also place their health on a visual analogue scale (VAS), for which 0 represents the worst imaginable health state and 100 the best imaginable health state. The UK social preference weights for EQ-5D-3L health states[57] were used to obtain single utility values from the responses.

TABLE 28 Unit costs (GBP) of health service contacts

Resource item	Unit cost (£)	Source
Primary admission		
Intensive care level 1 day	696.12	*NHS Reference Costs 2013–14*[49] (XC07Z) adult critical care
Intensive care level 2 day	932.10	*NHS Reference Costs 2013–14*[49] (XC06Z) adult critical care
Intensive care level 3 day	1440.64	*NHS Reference Costs 2013–14*[49] (XC01Z-XC05Z weighted average) adult critical care
Other ICU day	1228.65	*NHS Reference Costs 2013–14*[49] (XC01Z-XC07Z weighted average) adult critical care
HDU day	932.10	*NHS Reference Costs 2013–14*[49] (XC06Z) adult critical care
Ward bed-day	437.00	*NHS Reference Costs 2013–14*[49] (VC40Z) rehabilitation for respiratory disorders
80-mg simvastatin tablets, 28 tablets per pack	2.02	*NHS Electronic Drug Tariff*[51]
Other hospital services		
Non-specific ward days	483.04	*NHS Reference Costs 2013–14*[49] (weighted average length of stay and cost of non-elective long stays)
Outpatient attendance	109.00	*Unit Costs of Health and Social Care 2014*,[50] p. 111
Attendance at A&E	233.00	*Unit Costs of Health and Social Care 2014*,[50] p. 111 (see and treat and convey)
Community health services		
GP surgery consultation	46.00	*Unit Costs of Health and Social Care 2014*,[50] p. 195
GP telephone consultation	28.00	*Unit Costs of Health and Social Care 2014*,[50] p. 195
GP home consultation	115.00	*Unit Costs of Health and Social Care 2013*,[52] p. 191 (inflated using the hospital and community health services index)
GP out-of-hours consultation	115.00	*Unit Costs of Health and Social Care 2013*,[52] p. 191 (home visit unit cost assumed as above)
GP nurse surgery consultation	13.70	*Unit Costs of Health and Social Care 2014*,[50] p. 192 (per 15.5-minute surgery consultation)
GP nurse telephone consultation	4.85	*Unit Costs of Health and Social Care 2014*,[50] p. 192 (per 7.1-minute telephone consultation)[a]
GP nurse home visit	24.29	*Unit Costs of Health and Social Care 2014*,[50] p. 192 (per 15.5-minute consultation and 12-minute travel assumed[a])
District nurse home visit	39.00	*Unit Costs of Health and Social Care 2014*,[50] p. 187
Social worker visit	79.00	*Unit Costs of Health and Social Care 2014*,[50] p. 206 (per 1-hour cost assumed to include travel)
Physiotherapist visit	51.00	*Unit Costs of Health and Social Care 2014*,[50] p. 179
Occupational therapist visit	77.00	*Unit Costs of Health and Social Care 2014*,[50] p. 180
Dietitian visit	37.00	*Unit Costs of Health and Social Care 2014*,[50] p. 238 (with qualifications)
Nurse specialist visit	74.00	*Unit Costs of Health and Social Care 2014*,[50] p. 190 (per 1-hour cost assumed to include travel)
Rapid response/acute care episode	182.00	*Unit Costs of Health and Social Care 2013*,[52] p. 111 (inflated using the hospital and community health services index)
Psychotherapy/counselling	50.00	*Unit Costs of Health and Social Care 2014*,[50] p. 51
Day centre	38.00	*Unit Costs of Health and Social Care 2014*,[50] p. 38 (per client session)

TABLE 28 Unit costs (GBP) of health service contacts (*continued*)

Resource item	Unit cost (£)	Source
Care services		
Home help/care worker	17.00	*Unit Costs of Health and Social Care 2014*,[50] p. 210 (per 1-hour cost assumed to include travel)
Delivered meals	6.60	*Unit Costs of Health and Social Care 2014*,[50] p. 127 (per meal)
Nursing home	511.00	*Unit Costs of Health and Social Care 2014*,[50] p. 33 (per week)
Respite	511.00	Nursing home cost assumed as above
Residential care home	493.00	*Unit Costs of Health and Social Care 2014*,[50] p. 34 (weekly)
Sheltered housing	443.00	*Unit Costs of Health and Social Care 2014*,[50] p. 39 (extra care housing for older people, weekly)

A&E, accident and emergency; GBP, Great British pounds.
a The GP time estimates are assumed when not available for GP nurse.

The area under the curve method was used to estimate patient-specific QALYs accrued over the 12-month period. This method involves multiplying the utility of the patients' health state at a certain time point by the duration of the health state and then summing these over the study period. It was assumed that changes in utility over the time points were linear.

The EQ-5D-3L was administered at discharge, and at 3, 6 and 12 months post randomisation. All questionnaires were posted out to survivors, except for at discharge when it was administered face to face. As patients were unconscious and receiving invasive mechanical ventilation at the time of randomisation, baseline utility could not be measured. Instead we used the utility value for an unconscious state (–0.402) from the tariff.[57] This approach has been used previously in economic evaluations of therapies for patients with ARDS.[54,55]

Over the course of the trial it became apparent that many patients were still in hospital at 3 months and were then not administered the EQ-5D-3L at this time point. Furthermore, the timing of the discharge questionnaire varied from patient to patient. For these reasons QALYs were calculated using only baseline, 6- and 12-month utility scores in the first instance as these captured the complete study period. Discharge and 3 months were used in the QALY calculation in a sensitivity analysis.

To maximise the return rate of postal questionnaires, the following evidence-based strategies were introduced.

- Franked, addressed return envelopes were provided with each 3-, 6- and 12-month questionnaire.
- A 'thank-you' voucher to the value of £5 (or €5 for Ireland) was enclosed with the first questionnaire sent out.
- A covering letter from the trial manager was included with each questionnaire.
- A follow-up telephone call was made if the questionnaire was not returned with the offer to resend a copy of the questionnaire if needed.
- A second and final follow-up telephone contact was made as a final reminder.
- To minimise the risk of causing distress to the relation of a patient who died after leaving the hospital, the CTU contacted the patient's GP and NHS Digital to ascertain the patient's survival status prior to sending out any questionnaires.

Analysis and reporting

We undertook the following:

- analysis of service use and costs
- analysis of health outcomes
- cost–utility analysis.

Analysis of service use and costs

The analysis included all patients and their available data. We used mean imputation to impute missing data in cases for which the patient reported using a care service (e.g. carer, home help, delivered meals) but did not provide the number of contacts per week.

Death was not considered a censoring event in the primary analysis and periods after death were counted as observations with known outcome.[58] In practice, this meant that for patients who had died in hospital, costs after hospital discharge until 12-month follow-up were considered to be zero. For patients who were discharged from hospital but had died by 28 days, we also assumed that their costs after hospital discharge until 12 months were zero. This was an acceptable assumption because, out of the patients who were dead at 28 days (24.5%; 132/539), only two patients were discharged from hospital and they both subsequently died within 2 weeks of discharge. For patients who had died by 6 months, costs from 6 to 12 months were considered to be zero. In some cases, we could not assign zero costs to all periods after death. For patients who were discharged from hospital, alive at 28 days but had died by 6 months, costs from discharge to 6 months were considered to be missing as no information was available on their use of resources in the period up to their death. The same was true for patients alive at 6 months but had died by 12 months; costs from 6 to 12 months were treated as missing.

Descriptive statistics were used to summarise the health service resource use and associated costs for (1) primary admission, (2) discharge to 6 months and (3) 6 to 12 months. Differences in mean service use between groups were analysed using two-tailed independent *t*-tests and differences in proportions were analysed using two-tailed Fisher's exact test. Non-parametric bootstrapping was used to calculate 95% bootstrap CIs of differential mean costs, drawing 1000 samples of the same size as the original sample separately for each group with replacement.

Analysis of health outcomes

The analysis included all patients and their available data. Descriptive statistics were used to summarise EQ-5D-3L utilities, VAS scores and QALYs at discharge, 3, 6 and 12 months. Differences in utilities and VAS scores between groups were tested using two-tailed independent *t*-tests. Non-parametric bootstrapping was used to calculate 95% bootstrap CIs of differential mean QALYs. A utility of zero was assigned to patients who were dead at the relevant EQ-5D-3L collection time point (3, 6 and 12 months).

Cost-utility analysis

The analysis included only patients with complete cost and QALY data. The ICER was calculated as the difference in mean health service cost of the simvastatin and placebo groups divided by the difference in mean QALYs between the groups to establish the cost per QALY gained. To account for sampling uncertainty in the total cost and QALY data, non-parametric bootstrapping was performed to generate 1000 bootstrap replicates of the ICERs, which were then plotted on the cost-effectiveness plane. The resulting scatter plot was used to derive the cost-effectiveness acceptability curve (CEAC) by calculating the proportion of the replicates that would be considered cost-effective at various willingness-to-pay (WTP) thresholds for an additional QALY. In general, NICE[59] considers interventions with an ICER of < £20,000 to be cost-effective.

Cost-effectiveness acceptability curves were also constructed for the following sensitivity analyses:

- Multiple regression used to estimate the mean difference between groups for total health service costs and QALYs after adjusting for the baseline variables of age, APACHE II score and vasopressor requirement.
- Multiple imputation for missing data – missing total cost and QALY data points were filled simultaneously using imputation by chained equations and predictive mean matching to generate five imputed data sets. Treatment group, baseline APACHE II score, age, vasopressor requirement at baseline, mortality at 28 days, mortality at 12 months and primary admission costs were entered into the model as predictors of missing data.
- Multiple imputation and adjustment for baseline variables simultaneously.
- Death as a censored event (i.e. data were considered to be missing for patients who had died during the study period).
- Not using mean imputation for missing care service data (i.e. treated as missing).
- Using discharge and 3-month EQ-5D-3L data in the calculation of QALYs when available.

All curves were constructed regardless of whether or not the cost and effect differences were statistically significant, in keeping with current health economic practice.

All analyses were performed using Stata® (version 12.0; StataCorp LP, College Station, TX, USA) Intercooled (IC) for Windows® (Microsoft Corporation, Redmond, WA, USA). Costs and QALYs were not discounted as the time horizon of the study was 12 months. Significance ($p < 0.05$) was judged when the CI of differential means or QALYs excluded zero.

Results

A total of 540 patients were randomised. Five patients withdrew consent during the study but only one did not give permission for the use of their anonymised data collected prior to withdrawal. Thus, 539 patients were included in the health economics analysis: 259 in the simvastatin group and 280 in the placebo group. A total of 266 patients completed the discharge EQ-5D-3L: 131 (49%) in the simvastatin group and 135 (51%) in the placebo group. Out of the 367 patients alive at 3 months, 222 (60%) returned the questionnaire [114 (51%) in the simvastatin group and 108 (49%) in the placebo group]. Out of the 359 patients alive at 6 months, 213 (59%) returned the 6-month questionnaire [114 (32%) in the simvastatin group and 99 (27%) in the placebo group]. Out of the 349 patients alive at 12 months, 185 (53%) returned the 12-month questionnaire [91 (26%) in the simvastatin group and 94 (27%) in the placebo group]. A total of 158 (45%) patients completed both the 6- and 12-month questionnaires: 82 (23%) in the simvastatin group and 76 (22%) in the placebo group.

Analysis of service use and costs

Patients' use of services during their primary admission to hospital, including simvastatin, is presented in *Table 29*. As level of care was not recorded for days spent in ICU after 28 days, these data are presented separately. No differences were statistically significant.

Patients' use of other hospital services (hospital inpatient stay, outpatient attendances and accident and emergency visits) following discharge is presented in *Table 30*. Patients in the simvastatin group reported fewer hospital inpatient days but more outpatient and accident and emergency visits than the placebo group at both 6 and 12 months; however, these differences were not statistically significant between groups.

TABLE 29 Primary admission health service use by treatment group

	Treatment group				
	Simvastatin		Placebo		
Primary admission (baseline to discharge)	*n*	Mean (SD)	*n*	Mean (SD)	*p*-value
Primary ICU stay days	259	15 (13.41)	280	15 (12.5)	0.997
Intensive care level 1 days	259	0.53 (1.2)	280	0.46 (1.14)	0.451
Intensive care level 2 days	259	2.32 (2.85)	280	2.31 (3.1)	0.958
Intensive care level 3 days	259	10.66 (7.56)	280	10.77 (8.24)	0.866
Other ICU days[a]	257	1.00 (4.84)	275	1.19 (6.33)	0.695
HDU days[a]	257	0.82 (4.28)	275	1.75 (8.05)	0.098
Ward days[a]	257	13.91 (26.10)	275	12.21 (18.61)	0.285
Advanced respiratory support days	259	10.71 (7.55)	280	10.9 (8.33)	0.774
Advanced cardiovascular support days	259	2.03 (3.57)	280	2.31 (3.88)	0.379
Liver support days	259	0.01 (0.11)	280	0 (0)	0.071
Neurological support days	259	0.64 (2.56)	280	0.71 (2.64)	0.769
Renal support days	259	1.74 (4.1)	280	2.09 (4.56)	0.348
80-mg simvastatin tablets	259	19.93 (14.24)	–	–	–

a Seven patients had unobtainable hospital discharge dates.

Patients' use of community health services from baseline until 12 months is presented in *Table 31*. There were no statistically significant differences between the groups.

Patients' use of care services is presented in *Tables 32* and *33*. In the period from discharge to 6 months, mean imputation was used for three patients who used a home help, three patients who used a carer paid for by the health service and one patient who used delivered meals. For the patient who used delivered meals, the mean value from the 6- to 12-month period was imputed as only one patient reported using the service from discharge to 6 months. In the period from 6 to 12 months, mean imputation was used for four patients who used a carer paid for by the health service. Patients in the placebo group received statistically significantly more carer visits paid for by the health service between 6 and 12 months than those in the simvastatin group. All other differences were not significant.

Patients' use of private and informal carers is presented in *Table 33*. Private paid carers represent a cost to the patient rather than the health or social care provider and although they are not included in the subsequent ICER calculation, as they are outside the health-care provider perspective, they are presented for completeness. At 6 months, there was a statistically significant association between treatment and the use of unpaid carers, with a larger proportion of patients in the placebo group using unpaid carers.

Costs for individual resource components were grouped together to estimate mean costs for the primary hospital admission, other hospital services, community services and care-related services over the study period (*Table 34*). These total costs were calculated only for patients with complete data on each of the cost components. Lower mean costs were observed in the simvastatin group for all service types, with the exception of the primary hospital admission. The total mean cost difference at 12 months was statistically significant (–£4987, 95% CI –£10,060 to –£390). No other difference was statistically significant.

TABLE 30 Other hospital service use from baseline until 12 months by group [values are *n* (%) of patients using the service and mean (SD) use]

	Discharge to 6 months					6–12 months				
	Simvastatin (*N* = 179)		Placebo (*N* = 184)			Simvastatin (*N* = 168)		Placebo (*N* = 190)		
Other hospital service	*n* (%)	Mean (SD)	*n* (%)	Mean (SD)	*p*-value	*n* (%)	Mean (SD)	*n* (%)	Mean (SD)	*p*-value
Hospital inpatient days	18 (10.06)	0.99 (4.72)	21 (11.41)	1.28 (7.92)	0.675	18 (10.71)	0.89 (4.36)	20 (10.53)	0.99 (6.15)	0.857
Hospital outpatient appointment	73 (40.78)	1.72 (5.49)	54 (29.35)	1.36 (4.86)	0.506	51 (30.36)	1.03 (2.29)	43 (22.63)	0.84 (2.68)	0.467
Hospital accident and emergency visit	22 (12.29)	0.3 (1.43)	17 (9.24)	0.12 (0.4)	0.097	17 (10.12)	0.17 (0.65)	16 (8.42)	0.15 (0.59)	0.769

TABLE 31 Community health service use from baseline until 12 months by group [values are *n* (%) of patients using the service and mean (SD) use]

	Discharge to 6 months					6–12 months				
	Simvastatin (*N* = 179)		Placebo (*N* = 184)			Simvastatin (*N* = 168)		Placebo (*N* = 190)		
Service	*n* (%)	Mean (SD)	*n* (%)	Mean (SD)	*p*-value	*n* (%)	Mean (SD)	*n* (%)	Mean (SD)	*p*-value
GP surgery consultation	79 (44.13)	2.41 (4.57)	65 (35.33)	2 (4.46)	0.383	61 (36.31)	2.11 (6.35)	62 (32.63)	1.42 (2.84)	0.176
GP telephone consultation	28 (15.64)	0.72 (2.98)	25 (13.59)	0.74 (3.1)	0.927	18 (10.71)	0.93 (8.09)	17 (8.95)	0.44 (2.09)	0.414
GP home consultation	19 (10.61)	0.26 (1.45)	23 (12.5)	0.33 (1.29)	0.66	9 (5.36)	0.11 (0.54)	17 (8.95)	0.23 (0.93)	0.149
GP out-of-hours consultation	6 (3.35)	0.15 (1.51)	10 (5.43)	0.07 (0.33)	0.513	11 (6.55)	0.08 (0.31)	9 (4.74)	0.08 (0.41)	0.97
GP nurse surgery consultation	34 (18.99)	0.73 (2.56)	29 (15.76)	1.22 (5.3)	0.27	32 (19.05)	0.57 (1.74)	18 (9.47)	0.93 (7.36)	0.542
GP nurse telephone consultation	3 (1.68)	0.11 (1.14)	2 (1.09)	0.05 (0.61)	0.59	2 (1.19)	0.06 (0.59)	1 (0.53)	0.01 (0.07)	0.207
GP nurse home consultation	16 (8.94)	1.13 (5.56)	18 (9.78)	1.79 (12.32)	0.51	3 (1.79)	0.04 (0.29)	3 (1.58)	1.44 (9.82)	0.065
District nurse	1 (0.56)	0.02 (0.22)	5 (2.72)	0.23 (1.74)	0.107	1 (0.6)	0.14 (1.85)	2 (91.05)	0.04 (0.46)	0.469
Social worker	12 (6.7)	0.14 (0.73)	11 (5.98)	0.12 (0.52)	0.763	3 (1.79)	0.07 (0.64)	13 (6.84)	0.21 (1.19)	0.159
Physiotherapist	39 (21.79)	1.87 (5.25)	25 (13.59)	1.72 (8.41)	0.846	17 (10.12)	0.53 (2.16)	20 (10.53)	1.28 (6.5)	0.155
Occupational therapist	23 (12.85)	0.67 (2.78)	14 (7.61)	0.92 (8.42)	0.708	9 (5.36)	0.36 (2.74)	17 (8.95)	0.32 (1.66)	0.861
Dietitian	3 (1.68)	0.04 (0.32)	2 (1.09)	0.04 (0.43)	0.913	–	–	–	–	–
Nurse specialist	2 (1.12)	0.21 (2.62)	1 (0.54)	0.02 (0.22)	0.314	–	–	–	–	–
Rapid response	4 (2.23)	0.02 (0.15)	4 (2.17)	0.12 (1.41)	0.36	3 (1.79)	0.02 (0.13)	3 (1.58)	0.02 (0.18)	0.848
Psychotherapy/counselling	0 (0)	0 (0)	2 (1.09)	0.02 (0.16)	0.186	1 (0.6)	0.01 (0.08)	1 (0.53)	0.24 (3.26)	0.36
Day centre	–	–	–	–	–	3 (1.79)	0.17 (1.52)	1 (0.53)	0.05 (0.73)	0.357

TABLE 32 Care service use from baseline until 12 months by group [values are *n* (%) of patients using the service and mean (SD) use]

	Discharge to 6 months					6–12 months				
	Simvastatin (*N* = 179)		Placebo (*N* = 184)			Simvastatin (*N* = 168)		Placebo (*N* = 190)		
Care service	*n* (%)	Mean (SD)	*n* (%)	Mean (SD)	*p*-value	*n* (%)	Mean (SD)	*n* (%)	Mean (SD)	*p*-value
Home help visits	5 (2.79)	2.46 (16.16)	3 (1.63)	1.94 (15.53)	0.756	0 (0)	0 (0)	3 (1.58)	4.93 (54.39)	0.241
Delivered meals visits	1 (0.56)	0.77 (10.31)	0 (0)	0 (0)	0.311	0 (0)	0 (0)	3 (1.58)	2.19 (17.81)	0.112
Carer visits (paid by health-care provider)	10 (5.59)	7.52 (32.76)	10 (5.43)	13.05 (74.53)	0.363	6 (3.57)	5.42 (29.41)	14 (7.37)	24.46 (104.05)	0.023
Residential care home (days)	2 (1.12)	0.08 (1.05)	0 (0)	0 (0)	0.311	1 (0.6)	1.07 (13.89)	0 (0)	0 (0)	0.288
Nursing home (days)	4 (2.23)	1.36 (11.92)	4 (2.17)	0.62 (4.23)	0.427	1 (0.6)	1.07 (13.89)	0 (0)	0 (0)	0.288
Shelter (days)	1 (0.56)	0.04 (0.52)	2 (1.09)	2.63 (26.94)	0.199	1 (0.6)	0 (0)	3 (1.58)	1.89 (18.42)	0.183
Respite care (days)	2 (1.12)	0.3 (2.86)	1 (0.54)	0.15 (2.06)	0.568	0 (0)	0 (0)	1 (0.53)	0.07 (1.02)	0.348

TABLE 33 Private and informal carer use over the study period by group [values are *n* (%) of patients using the service and mean (SD) use]

	Discharge to 6 months			6–12 months		
	Treatment group			Treatment group		
	Simvastatin (*n* = 179)	Placebo (*n* = 184)		Simvastatin (*n* = 168)	Placebo (*n* = 190)	
Service	*n* (%)	*n* (%)	*p*-value	*n* (%)	*n* (%)	*p*-value
Paid carer	6 (3.35)	0 (0)	0.638	1 (0.60)	4 (2.11)	0.376
Unpaid carer	21 (11.73)	25 (13.59)	0.014	15 (8.93)	17 (8.95)	1.00

TABLE 34 Health services costs (GBP) over the study period by group

	Treatment group				
	Simvastatin		Placebo		
Service costs	*n*	Mean cost (SD) (£)	*n*	Mean cost (SD) (£)	Cost difference (95% CI):[a] intervention – control
Baseline to 6 months					
Primary admission	257	26,017.93 (19,825.31)	275	26,311.24 (20,162.46)	–293.31 (–3653.94 to 3161.23)
Other hospital services	179	738.19 (2517.87)	184	795.51 (3926.37)	–57.32 (–820.81 to 573.50)
Community health services	179	395.58 (776.44)	184	421.30 (1085.47)	–25.72 (–232.82 to 158.40)
Care-related services	179	304.29 (1164.08)	184	477.75 (2150.14)	–173.46 (–559.12 to 181.97)
6–12 months					
Other hospital services	168	579.49 (2215.12)	190	603.51 (3211.87)	–24.02 (–669.03 to 519.74)
Community health services	168	223.70 (682.05)	190	284.46 (671.16)	–60.76 (–207.01 to 80.69)
Care-related services	168	245.76 (1481.22)	190	639.32 (2810.66)	–393.56 (–870.93 to 36.91)
Total: baseline to 6 months	179	25,228.57 (16,640.52)	183	27,989.23 (21,313.84)	–2760.53 (–6694.82 to 1186.83)
Total: 6–12 months	168	1048.94 (3282.70)	190	1527.28 (5197.55)	–478.34 (–1472.50 to 377.68)
Total: 12-month health service costs	147	24,183.96 (16,969.87)	160	29,171.08 (24,967.77)	–4987.12 (–10,059.91 to –390.40)

GBP, Great British pounds.

a The CIs are based on 1000 bootstrap resamples. Significance is judged when the CI does not cross zero. Negative costs reflected cost savings in favour of the intervention.

Health outcomes analysis

Mean EQ-5D-3L utilities and VAS scores at discharge, 3, 6 and 12 months, and QALYs at 12 months are presented in *Table 35*. Patients in the simvastatin group had higher HRQoL at each time point than those in the placebo group, with the most notable difference at 6 months. No differences between the groups were statistically significant. Both groups experienced an overall decline between discharge and 12 months.

Cost–utility analysis

Results from the cost–utility analysis are presented in *Table 36*. Simvastatin is both less costly and more effective than placebo; thus, it is the dominant strategy with a mean difference in costs of –£3601 and a mean difference in QALYs of 0.064. In this situation, the ICER is not calculated as its magnitude does not convey any meaning.[58] Sampling uncertainty is represented by the joint distribution of the bootstrapped differences in cost and QALY on the cost-effectiveness plane for the primary analysis (*Figure 13*). The majority of the points lie below the *x*-axis (indicating that simvastatin is cost saving) and to the right of the *y*-axis (indicating simvastatin produces more QALYs than placebo). The small number of points lying outside of this area indicate a small degree of variability surrounding the presence and magnitude of cost savings and effectiveness.

The CEAC for the primary analysis presented in *Figure 14* summarises this uncertainty for the decision-maker and presents the probability of simvastatin being cost-effective compared with placebo at different thresholds of WTP per QALY gain for the primary and sensitivity analyses. The CEAC for the primary analysis indicates that, at a WTP threshold of £20,000 per QALY gain, the probability of simvastatin being cost-effective is 99%.

TABLE 35 The EQ-5D-3L utilities and VAS scores presented by instrument used and by treatment group

	Treatment group				
	Simvastatin		Placebo		
Health outcome	*n*	Mean score (SD)	*n*	Mean score (SD)	*p*-value
EQ-5D-3L utilities					
Discharge[a]	128	0.46 (0.38)	129	0.44 (0.37)	0.630
3 months	182	0.28 (0.38)	194	0.25 (0.37)	0.457
6 months	184	0.31 (0.38)	188	0.23 (0.36)	0.059
12 months	167	0.29 (0.37)	193	0.24 (0.37)	0.143
VAS scores					
Discharge[a]	126	61.09 (18.25)	133	56.73 (19.33)	0.064
3 months	183	37.03 (0.04)	200	32.25 (33.64)	0.168
6 months	191	38.03 (35.59)	192	31.76 (34.94)	0.083
12 months	172	34.01 (36.05)	197	29.60 (34.59)	0.233
QALYs	152	0.17 (0.27)	166	0.06 (0.26)	0.037

a The sample size is lower due to it being relevant only to patients who were discharged (i.e. did not die in hospital). For the other time points, the sample size includes patients who had died.

TABLE 36 Incremental costs and QALYs (with 95% CI) (associated ICERs and the probability of simvastatin being cost-effective compared with placebo at a threshold WTP per QALY of £20,000 for the base-case and sensitivity analyses)

Analysis	Incremental total health service costs (95% CI[a]) (£)	Incremental QALY gain (95% CI)	Probability of cost-effectiveness at £20,000 per QALY (%)
$n = 139$ for simvastatin, $n = 153$ for placebo[b]			
Primary analysis (unadjusted)	–3600.91 (–8061.10 to 859.28)	0.064 (0.002 to 0.127)	99
Adjusted for baseline variables	–2661.03 (–7842.76 to 2520.70)	0.089 (0.025 to 0.151)	95
$n = 259$ for simvastatin, $n = 280$ for placebo[c]			
Multiply imputed total costs and QALYs	–2132.69 (–5629.21 to 1363.83)	0.042 (–0.001 to 0.086)	96
Multiply imputed total costs and adjusted	–1290.35 (–5000.61 to 2419.91)	0.048 (0.005 to 0.091)	90
$n = 74$ for simvastatin, $n = 68$ for placebo[b]			
Death as a censoring event	–8532.48 (–16,107.75 to –957.21)	0.056 (–0.022 to 0.135)	99
$n = 137$ for simvastatin, $n = 151$ for placebo[b]			
No mean imputation of care data	–3966.00 (–8503.11 to 571.10)	0.06 (0.00 to 0.13)	99
$n = 138$ for simvastatin, $n = 150$ for placebo[b]			
QALY calculation using discharge and 3-month EQ-5D-3L	–3559.00 (–8241.41 to 1123.42)	0.084 (0.005 to 0.162)	99

a The CIs are based on 1000 bootstrap resamples.
b Sample sizes based on patients with complete data for both costs and QALYs.
c Sample sizes based on all patients because missing total costs and QALYs have been imputed.

Sensitivity analyses were conducted to determine the impact of changing particular assumptions on the cost-effectiveness (see *Table 36*). Although there are some notable effects on differential mean costs and effects, the CEACs for the sensitivity analyses (see *Figure 14*) indicate that cost-effectiveness of simvastatin was robust to these changes in the assumptions, with the probability of it being cost-effective at £20,000 per QALY never dropping below 90%.

Health economic discussion

The principal finding of the economic evaluation is that simvastatin compared with placebo was associated with lower costs and a significant QALY gain. Although the gain in QALYs was small (0.064; equivalent to 23 days of full health), it was associated with a cost saving equating to £3601 over the 12-month period. These findings were robust to changes in the methodological assumptions. Thus, simvastatin has a very high probability of being cost-effective at 1 year.

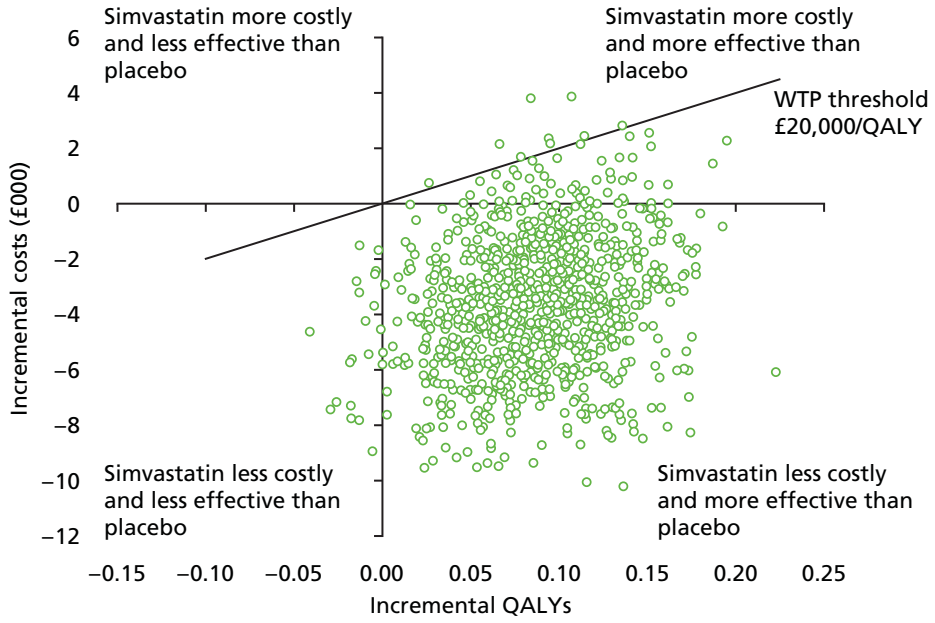

FIGURE 13 Cost-effectiveness plane for the primary cost-effectiveness analysis (showing bootstrapped replications of mean incremental costs and QALY gain and the WTP threshold of £20,000 per QALY).[44]

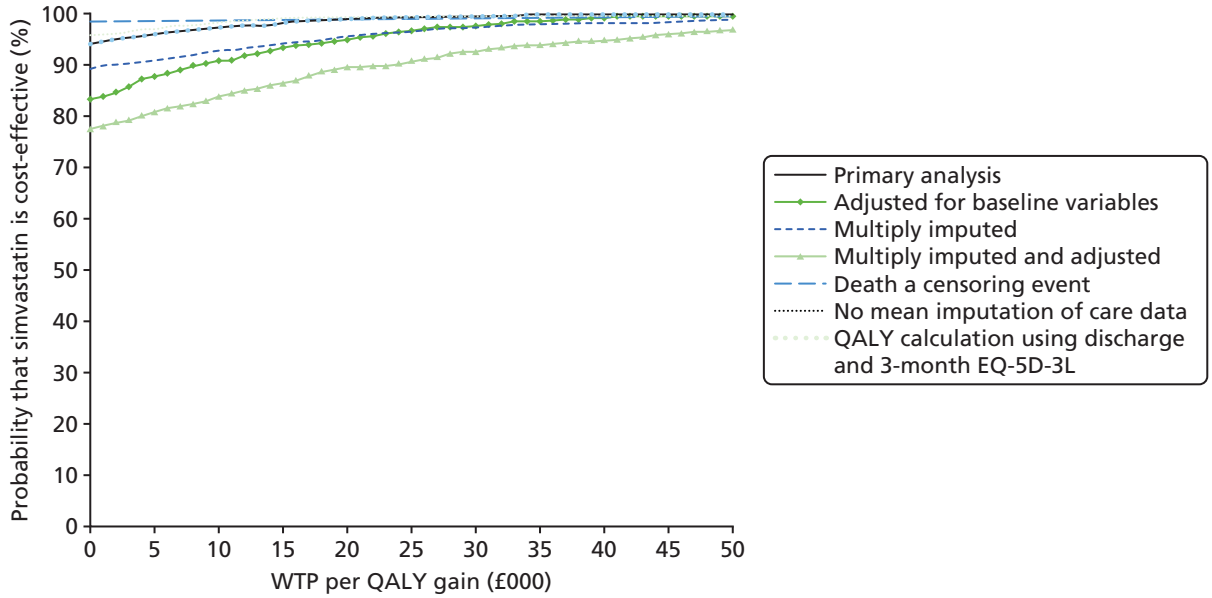

FIGURE 14 Cost-effectiveness acceptability curve (showing the probability of simvastatin being cost-effective compared with placebo for the primary and sensitivity analyses). Amended from Agus *et al.*[44] This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

There is currently no consensus on what constitutes a minimally important difference in mean QALYs between groups;[60] however, 0.05 has been suggested previously.[60,61] The difference observed in our analysis exceeds this, suggesting that the small difference is still meaningful. The small gain in QALYs is consistent with the modest and non-significant benefits observed in the clinical outcomes reported in *Chapter 3*. As all patients were assigned the same utility score at baseline, the difference in QALYs is due to the HRQoL of simvastatin patients being higher than placebo patients at both 6 and 12 months.

The majority of differences in individual resource use components were not statistically significant. However, when costs were categorised as primary admission, other hospital health services, community health services and care-related services, differences were more apparent. All other costs after discharge were lower in the simvastatin group, with the most notable cost savings associated with care-related services. The results corroborate with the HRQoL analysis. Patients in the placebo group experienced poorer health than those in the simvastatin group over the study period and this had an impact on their use of health services, including some services not paid for by the health services that were not included in the analyses.

There were a number of limitations to the economic evaluation. The study was powered to detect statistically significant differences in the primary outcome and not in costs, QALYs or cost-effectiveness. However, this is typically the case and significance rules are not typically relied on in the interpretation of cost-effectiveness analyses,[62] as greater emphasis is placed on the joint distribution of cost and effects. Nonetheless, having a sufficiently powered study would have led to more conclusive results[60] and allowed decision-makers to be more confident in the value claim.[58] There are limitations to this study related to the inevitable difficulties of collecting follow-up data from patients recovering from a stay in critical care. A substantial proportion of patients was lost to follow-up in the economic analysis. The cost–utility analysis included only patients with complete cost and QALY data but, of those alive at 12 months, only 45% completed both the 6- and 12-month follow-up questionnaires and some data were missing from these completed questionnaires. Previous intensive care trials[54,55] have also found it difficult to achieve high rates of long-term data collection and the experience of the HARP-2 trial confirms that this is a difficult population to follow up. Furthermore, economic data are particularly likely to be missing owing to the reliance on multiple components within HRQoL and resource use questionnaires required for the calculation of QALYs and costs. As a result, the cost–utility analysis was performed on a subgroup of patients with complete cost and QALY data. The utilities derived from the discharge and 3-month EQ-5D-3L were not used in the QALY calculation for the primary analysis. This was due to the variable timing of the discharge questionnaire and the fact that the 3-month questionnaire was not consistently administered to survivors if they were still hospital inpatients. A sensitivity analysis included them in the QALY calculation when they were available and there was a minimal impact on the overall results. The probability of simvastatin being cost-effective at a WTP threshold of £20,000 remained 99%.

Conclusion

Simvastatin was found to be cost-effective at 1 year compared with placebo for the treatment of ARDS, being associated with both a significant QALY gain and a cost saving. The cost-effectiveness remained robust to changes in methodological assumptions. However, given that the health economic analysis was performed on a subgroup of patients and the QALY gain was relatively small, there are currently insufficient data to support the treatment of patients with ARDS with simvastatin in the NHS.

Chapter 5 Overall discussion and conclusion

Despite promising findings for statins in ARDS in early-phase clinical trials, this large, multicentre, double-blind, randomised, placebo-controlled clinical trial found that high-dose enteral simvastatin was not effective at improving clinical outcomes in patients. Mortality rates were lower in the simvastatin group although this difference was not statistically significant. Simvastatin was associated with an increase in AEs, but there was no increase in SAEs. Simvastatin did not modulate mechanisms implicated in the development of ARDS. Simvastatin was found to be cost-effective at 1 year compared with placebo for the treatment of ARDS, being associated with a cost saving and small QALY gain. However, these were secondary outcomes and the cost–utility analysis was performed in a subgroup of patients.

The results do highlight the importance of undertaking a health economic analysis in the setting in which the primary clinical outcome is not significantly different between the trial arms. In addition, it flags important issues regarding the use of short-term clinical outcomes, such as VFDs, which have been shown to poorly correlate with long-term patient-centred outcomes such as long-term mortality[63] and QALYs.[63,64] The HARP-2 trial is considered a negative trial to the absence of a significant difference in the primary outcome (VFDs) at 28 days. However, it did achieve a non-significant 5% reduction in mortality and the cost–utility analysis found a significant QALY gain with a non-significant cost saving at 12 months. In the setting of no significant difference in mortality or other clinical outcomes, it is unlikely that the results of the cost-effectiveness analysis will be sufficient to change clinical practice. Had the trial been powered sufficiently for long-term mortality or QALYs, a different conclusion may have been reached. QALYs may be a feasible patient-centred primary outcome for critical care studies as they combine both morbidity and mortality, and have potential gains in statistical power owing to being a continuous variable.[61] Undoubtedly, more work is required to identify valid surrogate outcomes that more closely track patient outcomes.

The definition of ARDS uses a trade-off between feasibility and reliability.[65] Although the ARDS definition identifies clinical phenotypes with predictive validity,[66] owing to the underlying biological differences within the overall clinical phenotype, pharmacological interventions may only be effective in a subpopulation of the overall cohort of patients with ARDS in a RCT.[46,67] In support of our hypothesis, using a combination of eight plasma biomarkers and clinical data, Calfee *et al.*[46] recently identified ARDS subphenotypes that respond differently to differing ventilator strategies using latent class analysis methodology. This study prompted a call for further confirmatory research of this concept and other methods that explore ways to increase the signal-to-noise ratio.[68]

Our study was powered to detect a VFD of 2.6 days as the primary outcome. The mean VFD difference between the simvastatin and placebo groups was only 1.1 days, although the upper 95% CI was 2.8 days. Therefore, it is possible that a treatment effect may be present and that a subpopulation within the overall cohort may exist that has a more marked response to statins. It is possible that there is heterogeneity in treatment effect by baseline risk.[67] Thus, identifying ARDS endotypes (subsets with distinct pathophysiological mechanisms) that are more likely to benefit from targeted interventions informed by endotype characteristics is a research priority.

There are many challenges in undertaking a large clinical trial of a pharmacological treatment in patients with ARDS. Given the number of exclusion criteria that exist in any clinical trial, which are designed to include a study population that may benefit from the therapeutic intervention but exclude patients who are unlikely to benefit owing to their underlying condition or who are at increased risk of a complication from the intervention, there is often a high number of patients who are screened who are not eligible. This was approximately 10 : 1 in this study, which is similar to other ARDS trials.[12] This represents a considerable workload and should be considered when setting up such trials.

Surprisingly, the appropriate clinical outcome or set of clinical outcomes to use in a trial recruiting patients with ARDS requiring mechanical ventilation in ICU to date has not been defined. It may be that the VFDs was not the best outcome given that it is a composite outcome combining death and duration of ventilation, and gives similar weight in terms of the outcome to death and being ventilated for 28 days.

Several challenges were identified in relation to progressing sites through the contract completion stage prior to opening as a HARP-2 trial site; a number of sites would not accept the standardised version of the model Clinical Trial Agreement (mCTA) and requested several amendments, which slowed the contracting process and delayed the opening of new sites. In addition, it was also noted that a number of R&D offices completed the review of the mCTA to sign-off stage before they commenced the R&D review, rather than progressing both elements in tandem to speed up the approval process and allow sites to open quicker. To speed up the mCTA sign-off and R&D process, the trial manager telephoned the contract signatory and R&D office on a weekly basis for an update on progress. In addition, the trial co-ordinator hand-delivered the mCTA, Material Transfer Agreement and financial agreement to local signatories for signature, to speed up the local signature process.

To maintain enthusiasm for the study and combat trial fatigue, the following measures were introduced during the lifetime of the study.

- A review of site recruitment took place on a regular basis to identify under-recruiting sites. These sites were contacted and offered full support and assistance from the HARP-2 trial team to help them meet their target recruitment. This review led to the closure and replacement of five under-recruiting sites.
- A HARP-2 trial newsletter was created and circulated to sites on a quarterly basis.
- A research nurse phone-in was organised on a weekly basis to allow a one-to-one discussion with the trial co-ordinator.

A key strength of this study is the successful long-term follow-up of patients who have been discharged from critical care to assess their survival, HRQoL and resource use. However, we did find it difficult to achieve high rates of long-term follow-up data collection, in keeping with previous intensive care trials,[54,55] and a considerable amount of staff resource was involved in delivering this aspect of the trial. It is important to identify barriers to follow-up in these patients to inform future critical care studies.

Another potential barrier is the reliance on recall questionnaires at 6 and 12 months, without the provision of a service-use log or aide memoire at hospital discharge. Logs not only help patients keep track of their service use, making recall less daunting or onerous, but they may also help the patient continue to feel engaged in the trial after hospital discharge.

Chapter 6 Implications for health care

Simvastatin is not effective in improving clinical outcomes in patients with ARDS, although the use of simvastatin in critically ill patients does not appear to be associated with serious adverse effects. These results do not provide support for the use of simvastatin in the management of ARDS. However, these data indicate that simvastatin may be used in critically ill patients with a coexisting condition in which a statin is normally indicated (e.g. coronary heart disease).

This study has informed guidance in the Scandinavian clinical practice guideline on fluid and drug therapy in adults with ARDS, which recommended that statins are not used in the treatment of ARDS.[69]

Furthermore, this work has been included in two systematic reviews of randomised clinical trials in critically ill patients with severe sepsis, which concluded that statin therapy should not be recommended in the management of ARDS or severe sepsis in critically ill patients.[70,71]

Chapter 7 Implications for research

This work has the following implications for research.

- There is a need to define and validate surrogate outcomes used in early-phase critical care studies as well as their statistical analysis, which can accurately predict responses in patient-centred outcomes. This work is ongoing: www.comet-initiative.org/studies/details/709 (accessed 9 February 2017).[72]
- There is a need to confirm if ARDS endotypes (subsets with distinct pathophysiological mechanisms) that are more likely to benefit from targeted treatment with simvastatin (or indeed other interventions) exist.
- There is a need to define a core set of clinical outcomes to use in trials recruiting patients with ARDS requiring mechanical ventilation in an ICU. Furthermore, it is important that outcome measures are defined and standardised. This work is ongoing: www.comet-initiative.org/studies/details/709 (accessed 9 February 2017).[72,73]
- The framework for making health-care decisions based on health economic analyses, particularly in the absence of effects on clinical outcomes, in studies of patients with ARDS needs to be developed.
- The potential role of simvastatin in the prevention of ARDS in patients at high risk of developing ARDS (e.g. in surgical cohorts) has not yet been evaluated.

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Daniel F McAuley conceived the study.

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Daniel F McAuley and **John G Laffey** managed the undertaking of the trial with the CTU staff.

Daniel F McAuley, **John G Laffey**, **Gavin D Perkins**, **Brian Mullan**, **Thomas J Trinder**, **Paul Johnston**, **Phillip A Hopkins** and **Andrew J Johnston** contributed substantially to patient recruitment and data collection.

Lynn Murphy, **Christine McNally** and **Colette Jackson** managed the study and contributed to the review of the manuscript.

Clíona McDowell was the study statistician, **Ashley M Agus** was the health economist and **Daniel F McAuley**, **John G Laffey** and **Cecilia M O'Kane** interpreted the data.

Daniel F McAuley wrote the first draft of the manuscript and all authors reviewed and approved this final version of the manuscript.

All authors made a substantial contribution to the protocol development.

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Publications

McAuley DF, Laffey JG, O'Kane CM, Cross M, Perkins GD, Murphy L, *et al.* Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in acute lung injury to reduce pulmonary dysfunction (HARP-2) trial: study protocol for a randomized controlled trial. *Trials* 2012;**13**:170.

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Data sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data may be granted following review.

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Appendix 1 Serious adverse event listing

Treatment	Site	Subject number	SAE ID	Date of report	Date of onset	Date of resolution	Ongoing	SAE expected	Causality	SerAdvClass	Date drug started	If discontinued, date stopped	Patient withdrawn as a result	Study drug administered according to protocol
Simvastatin	s01	11,015	1	13 May 2011	13 May 2011	9 June 2011	No	No	Unrelated	Cardiac disorders	30 April 2011	3 May 2011	No	Yes
Simvastatin	s01	12,493	1	10 December 2013	9 December 2013	UNOB	Yes	No	Unrelated	Gastrointestinal	6 December 2013	9 December 2013	No	Yes
Simvastatin	s07	11,618	1	27 June 2012	14 June 2012	UNOB	Yes	No	Unrelated	Renal and urinary disorders	22 May 2012	28 May 2012	No	Yes
Simvastatin	s13	11,291	1	14 October 2011	14 October 2011	14 October 2011	No	No	Unlikely	Cardiac disorders	20 September 2011	17 October 2011	No	Yes
Simvastatin	s45	11,270	1	17 November 2011	16 November 2011	UNOB	Yes	No	Unrelated	Cardiac disorders	UNOB		No	No
Simvastatin	s45	11,458	1	6 February 2012	3 February 2012	3 February 2012	No	No	Unrelated	Gastrointestinal disorders	31 January 2012	26 February 2012	No	Yes
Simvastatin	s45	11,458	1	7 March 2012	5 March 2012	7 March 2012	No	No	Unrelated	Infections and infestations	31 January 2012		No	No
Simvastatin	s45	11,460	1	2 April 2012	31 March 2012	18 April 2012	No	No	Unrelated	Injury, poisoning and procedural complications	30 March 2012		No	Yes
Simvastatin	s45	11,844	1	29 October 2012	26 October 2012	UNOB	Yes	No	Unrelated	Nervous system disorders	10 October 2012	17 October 2012	No	Yes
Simvastatin	s51	11,033	1	14 March 2011	9 March 2011	21 March 2011	No	Yes	Probable	Musculoskeletal and connective tissue disorders/ elevated creatinine kinase	15 February 2011	9 March 2011	Yes	Yes
Simvastatin	s58	11,516	1	10 May 2012	9 May 2012	18 July 2012	No	Yes	Unlikely	Respiratory, thoracic and mediastinal disorders	27 April 2012	10 May 2012	Yes	Yes
Simvastatin	s60	12,354	1	2 August 2013	1 August 2013	1 August 2013	No	No	Unrelated	Gastrointestinal disorders	25 July 2013	UNOB	No	Yes
Placebo	s01	11,016	1	18 May 2011	17 May 2011	19 May 2011	No	No	Unrelated	Cardiac disorders	26 April 2011	24 May 2011	No	Yes
Placebo	s01	11,434	1	13 March 2012	13 March 2012	UNOB	Yes	No	Unrelated	Respiratory, thoracic and mediastinal disorders	3 February 2012		No	Yes

Treatment	Site	Subject number	SAE ID	Date of report	Date of onset	Date of resolution	Ongoing	SAE expected	Causality	SerAdvClass	Date drug started	If discontinued, date stopped	Patient withdrawn as a result	Study drug administered according to protocol
Placebo	s01	11,434	1	9 February 2012	8 February 2012	17 February 2012	No	No	Unrelated	Respiratory, thoracic and mediastinal disorders	3 February 2012	21 February 2012	No	No
Placebo	s01	11,436	1	22 February 2012	21 February 2012	22 February 2012	No	No	Unrelated	Cardiac disorders	21 February 2012	22 February 2012	No	Yes
Placebo	s38	12,586	1	3 October 2013	2 October 2013	2 October 2013	No	No	Unlikely	Cardiac disorders	1 October 2013		No	Yes
Placebo	s43	12,745	1	19 March 2014	8 March 2014	8 March 2014	No	No	Unrelated	Injury, poisoning and procedural complications	6 March 2014		No	Yes
Placebo	s43	12,745	1	11 April 2014	2 April 2014	3 April 2014	No	No	Possible	Nervous system disorders	6 March 2014	29 March 2014	No	Yes
Placebo	s45	11,730	1	4 May 2012	4 May 2012	UNOB	Yes	Yes	Unlikely	Hepatobiliary disorders	3 May 2012	4 May 2012	No	Yes
Placebo	s45	11,733	1	16 July 2012	15 July 2012	23 July 2012	No	No	Unrelated	Respiratory, thoracic and mediastinal disorders	20 June 2012	10 July 2012	No	Yes
Placebo	s47	11,578	1	31 May 2012	27 May 2012	UNOB	Yes	Yes	Possible	Musculoskeletal and connective tissue disorders/ elevated creatinine kinase	18 May 2012	27 May 2012	Yes	Yes
Placebo	s48	12,442	1	5 November 2013	4 November 2013	5 November 2013		No	Unlikely	Cardiac disorders	4 November 2013		No	Yes
Placebo	s58	11,519	1	11 July 2012	6 July 2012	12 July 2012	No	No	Unrelated	Infections and infestations	16 June 2012	27 June 2012	No	Yes
Placebo	s59	11,699	1	25 July 2012	22 July 2012	27 July 2012	No	No	Possible	Nervous system disorders	20 July 2012	26 July 2012	No	Yes
Placebo	s60	11,572	1	28 May 2012	25 May 2012	UNOB	Yes	No	Unrelated	Cardiac disorders	16 May 2012		No	Yes
Placebo	s61	11,089	1	20 June 2011	11 June 2011	02 July 2011	No	No	Unrelated	Infections and infestations	19 May 2011	4 June 2011	No	Yes
Placebo	s70	12,023	1	1 February 2013	31 January 2013	UNOB	Yes	No	Unlikely	Respiratory, thoracic and mediastinal disorders	14 January 2013	22 January 2013	No	Yes

ID, identification; SerAdvClass, serious adverse event classification; UNOB, unobtainable.

EME
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HTA
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